

PART I: STUDIES ON THE SYNTHESIS OF GIBBERELLINS  
PART II: THE STRUCTURE OF A TRIMER OF ISOPHORONE

A THESIS

Presented to  
The Faculty of the Division  
of Graduate Studies

By  
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In Partial Fulfillment  
of the Requirements for the Degree  
Doctor of Philosophy  
in the School of Chemistry

Georgia Institute of Technology  
March, 1977

PART I: STUDIES ON THE SYNTHESIS OF GIBBERELLINS  
PART II: THE STRUCTURE OF A TRIMER OF ISOPHORONE

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## ACKNOWLEDGMENTS

The author wishes to express his appreciation to all of those in the research group who gave both emotional and material support during the work on this thesis. Special thanks must go to Prof. House, whose insistence on excellence made the whole experience worthwhile.

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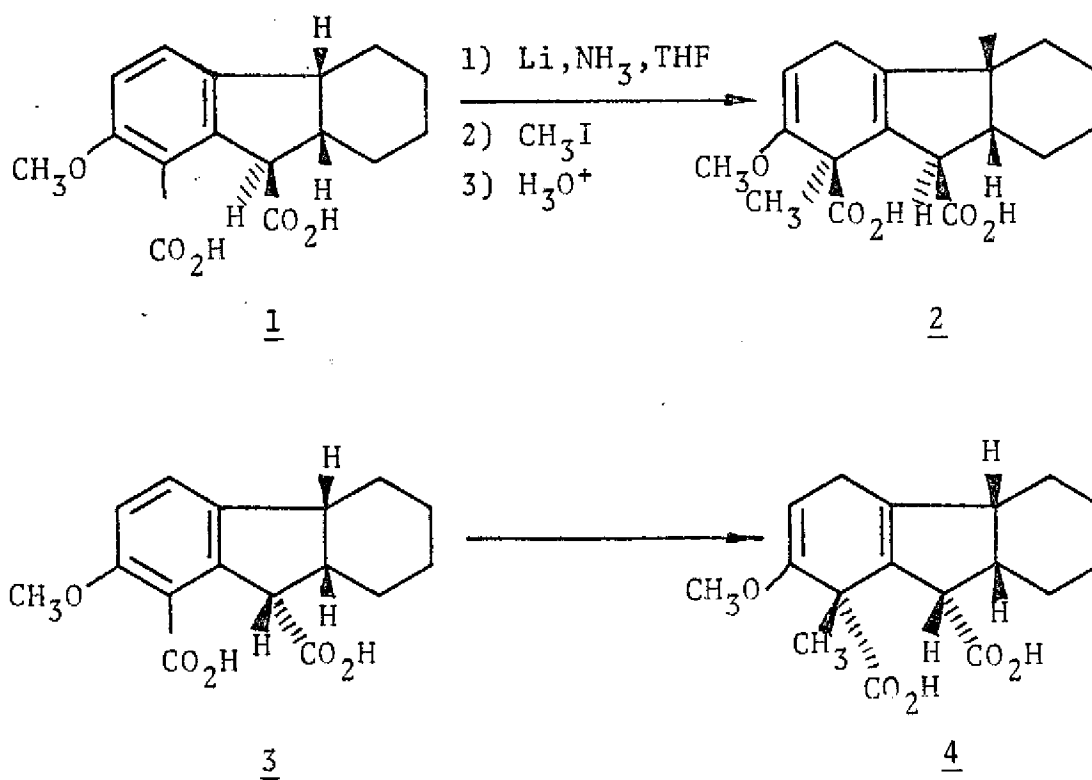
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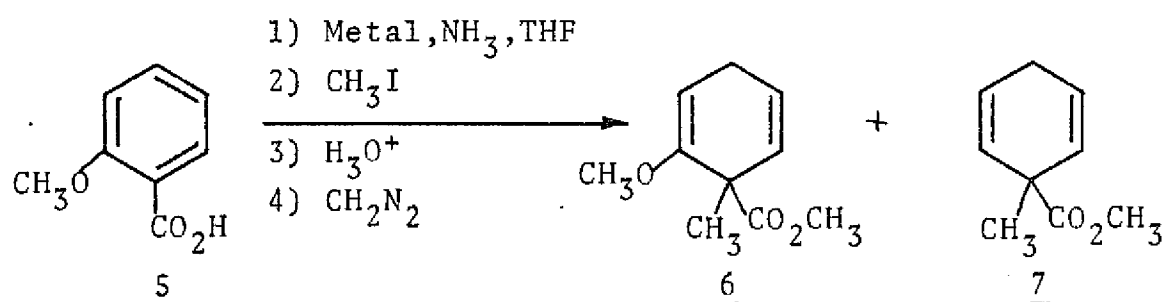
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## SUMMARY

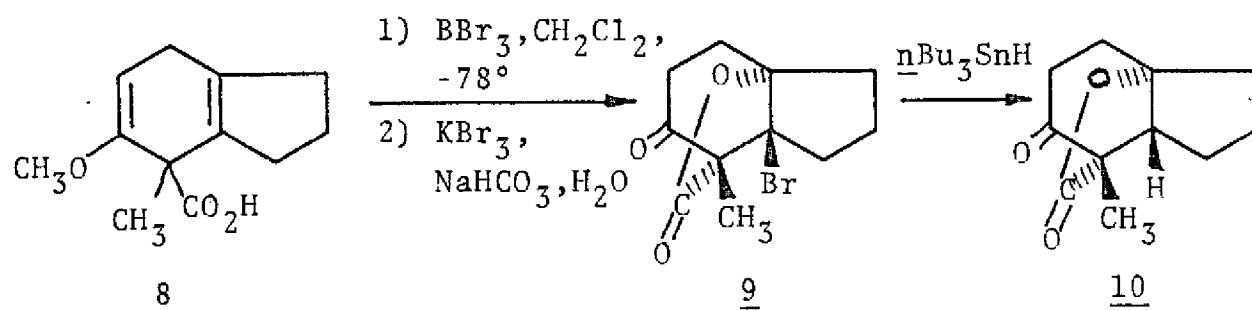
In a study of synthetic routes to gibberellins, application of the reduction-methylation sequence to the aromatic diacids 1 and 3 gave the syn diacids 2 and 4. The two diacids 2 and 4 each formed an unstrained six membered cyclic anhydride. When applied to the acid 5, the same sequence of reactions followed by esterification gave a



mixture of esters 6 and 7. Less of the ester 7 was formed with Na than with Li metal. The reduced acid 8 was converted



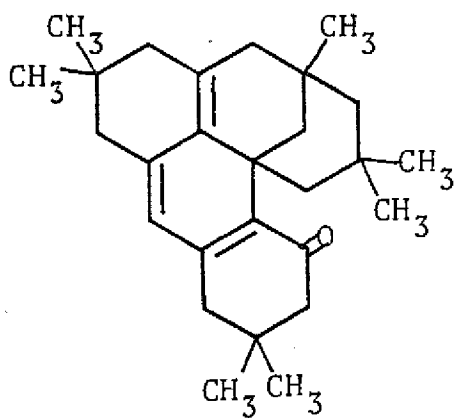
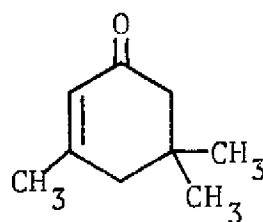
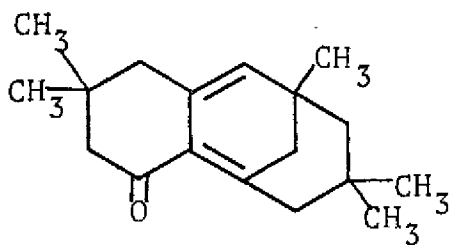
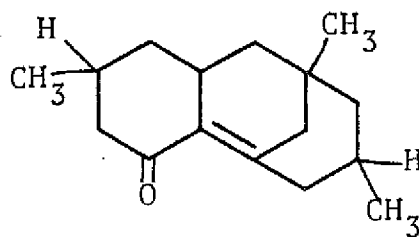
to the keto lactone 10 via the intermediate bromolactone 9.



A compound of chemical formula  $\text{C}_{27}\text{H}_{38}\text{O}$  formed by the base catalyzed self-condensation of isophorone was shown to have structure 11 by total synthesis. The method of synthesis provided strong evidence that a mechanism involving Michael addition of an enolate of isophorone (12) to the bridgehead enone 13 is involved in the formation of compound



11. Evidence was provided for the formation of the bridge-head enone 14.

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## CHAPTER I

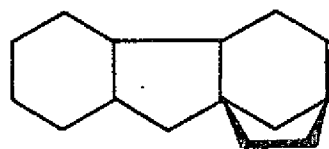
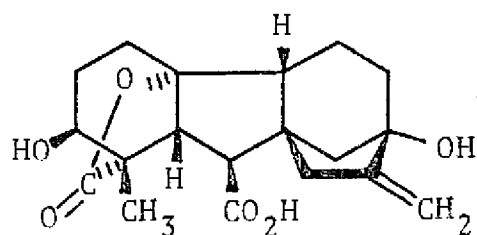
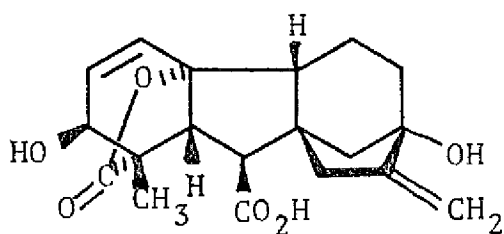
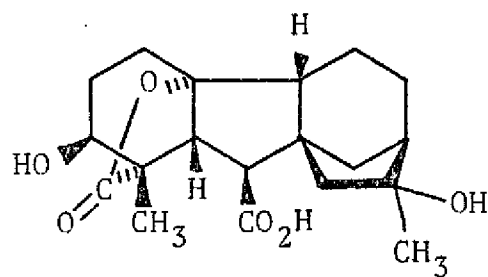
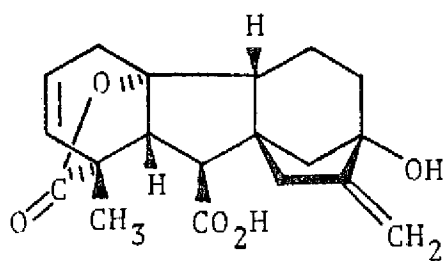
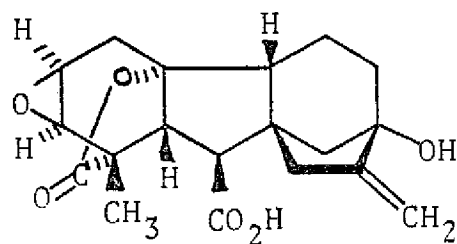
SURVEY OF SYNTHETIC APPROACHES TO THE A RING  
OF GIBBERELLINS

The gibberellins are a class of plant growth regulators which have the gibbane skeleton (1) (scheme I). The first compounds of this class were isolated in the 1930's, and the structures were elucidated during the 1950's and early 1960's, mainly from work on the readily available gibberellins A<sub>1</sub>(2) and A<sub>3</sub>(3, gibberellic acid).<sup>1</sup> Further examples are gibberellins A<sub>2</sub>(4), A<sub>5</sub>(5), A<sub>6</sub>(6), and A<sub>9</sub>(7), all of which are C<sub>19</sub> gibberellins.

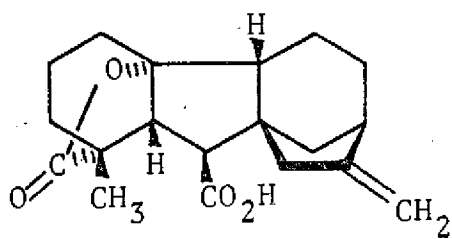
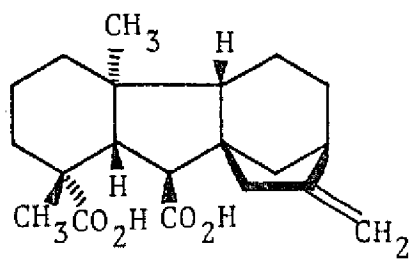
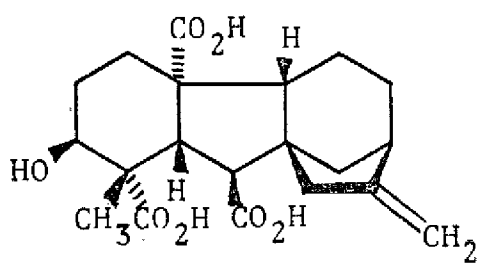
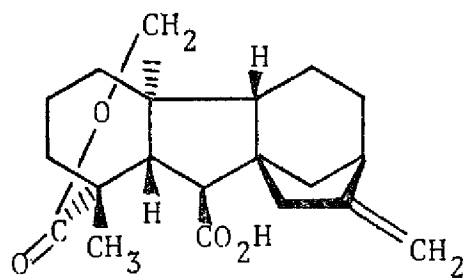
During biosynthetic studies, Cross and Norton discovered compounds similar to the C<sub>19</sub> gibberellins which had gibberellin like activity and which they believed were biosynthetic precursors to the C<sub>19</sub> gibberellins.<sup>2</sup> This view was also supported by later experiments.<sup>3</sup> These compounds are structurally related to the C<sub>19</sub> gibberellins, but differ in that they have one more carbon in the basic skeleton. Examples of the C<sub>20</sub> gibberellins are gibberellin A<sub>12</sub>(8), A<sub>13</sub>(9), and A<sub>15</sub>(10). To date, about 40 different gibberellins, including both C<sub>19</sub> and C<sub>20</sub> compounds, have been discovered.<sup>1d</sup>

On a cellular level, it is believed that gibberellins are responsible mainly for cell elongation processes, and at

Scheme I

123456

## Scheme I (cont.)

78910

least three general mechanisms for their action have been proposed from the available evidence.<sup>4</sup> (1) Gibberellins interact with the DNA in the cell nucleus and stimulate the synthesis of messenger RNA. The messenger RNA then promotes the synthesis of the various enzymes responsible for the cellular activity leading to growth. (2) Gibberellins in some way increase the permeability of membranes binding enzymes to the cell walls. The enzymes then diffuse into the cell and stimulate various growth processes. (3) Gibberellins stimulate the production of another plant growth regulator, auxin (indole acetic acid), by stimulating in some manner the production of hydrolyzing enzymes which digest proteins to amino acids. The tryptophan thus produced serves as a precursor to auxin. In addition, gibberellins may also affect peroxidase activity. Peroxidase is believed to regulate the level of auxin in the cell.

Because of the complexity of the structures found in the gibberellin family of compounds, synthetic efforts in this area have mainly involved the study of model compounds, and only rarely does one read of the completion of a total synthesis.<sup>5</sup> Several model studies of A ring syntheses have appeared, as well as a few studies which have been a part of much more extensive synthetic efforts; and they reflect the varying complexities found in the A rings themselves, from the relatively simple structures of gibberellins A<sub>9</sub>(7) and A<sub>12</sub>(8) to the more complex system of gibberellic acid (3).

Some of these studies will be surveyed in this chapter.

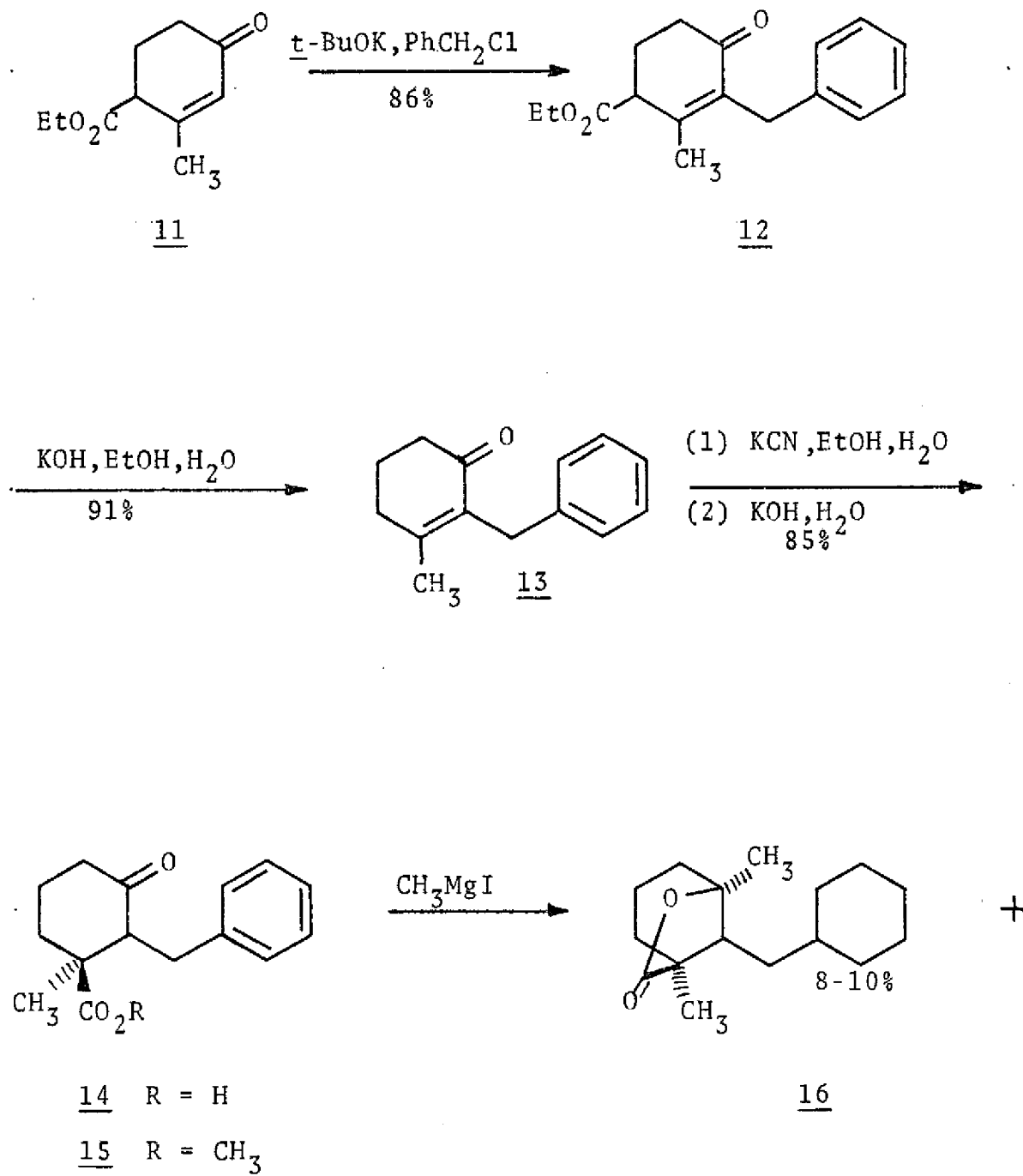
### C<sub>20</sub> Gibberellins

Ghatak and coworkers have explored several routes to the A ring of C<sub>20</sub> gibberellins. In their first approach<sup>6</sup> (scheme II), Hagemann's ester (11) was alkylated, hydrolyzed, and decarboxylated to give the unsaturated ketone 13. After Michael addition of cyanide followed by hydrolysis to the acid 14, addition of CH<sub>3</sub>MgI to the corresponding ester gave mainly the hydroxy ester 17. Hydroxy ester 17 was cyclized with acid, and the ester was hydrolyzed to give the tricyclic acid 18. The stereochemistry of 18 was proven by Tahara and Hoshino, who prepared a mixture of 18 and 21 from abietic acid (20).<sup>7</sup> They then completed an unambiguous synthesis of 21 by a different route.

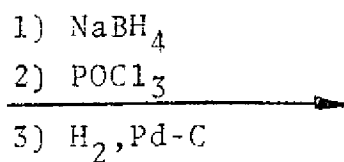
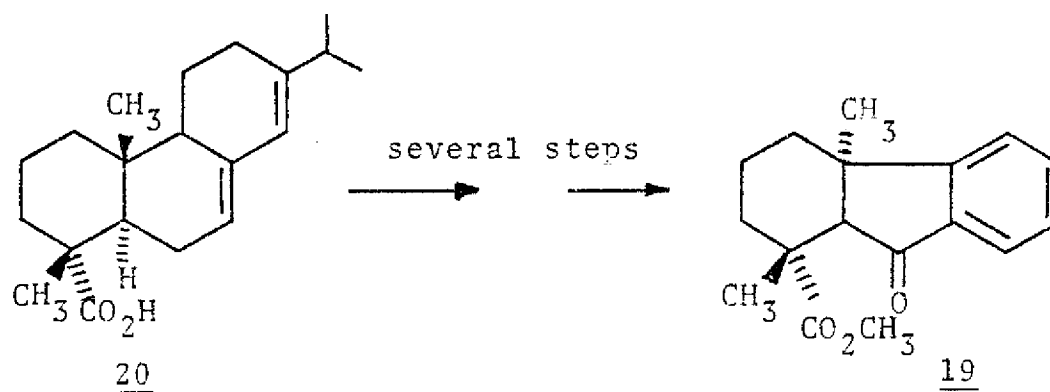
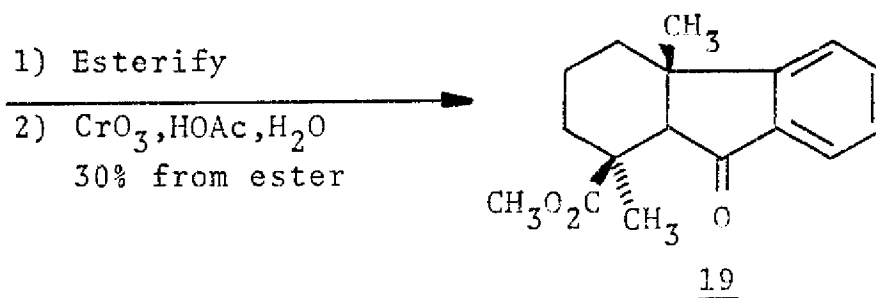
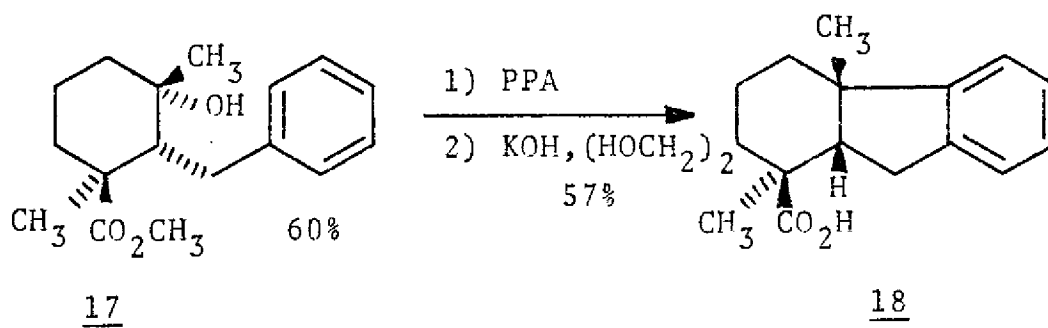
Two groups have studied the functionalization of the angular methyl group in compounds similar to the acids 18, 19, and 21. Mori and Matsui prepared the amide 22 (scheme II) and photolyzed it in the presence of Pb(OAc)<sub>4</sub> and I<sub>2</sub> according to the method of Barton.<sup>8</sup> They obtained a mixture of products from which 8-10% of the lactone 23 and 2-3% of the desired lactone 24 were isolated.<sup>9</sup> Cross and Gatfield performed a similar reaction on the amide 27, prepared from the lactone 25 as shown in scheme II, and obtained the lactone 28.<sup>10</sup>

The second approach explored by Ghatak is shown in scheme III.<sup>11</sup> The cyclobutanones 30 were prepared from the

## Scheme II

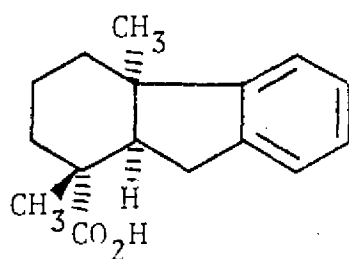


## Scheme II (cont.)

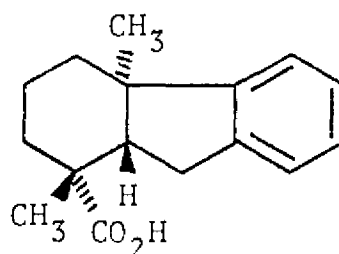
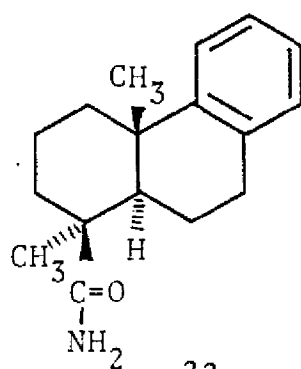
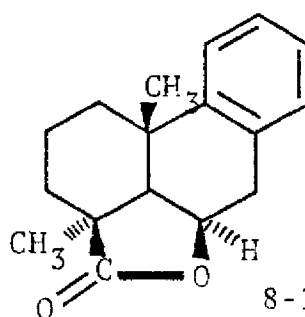
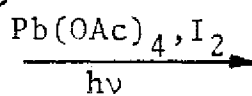




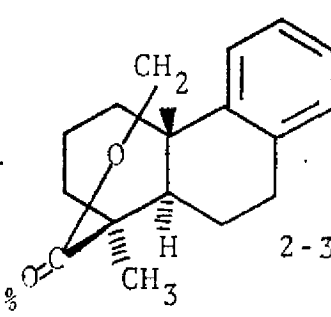
## Scheme II (cont.)

18

+

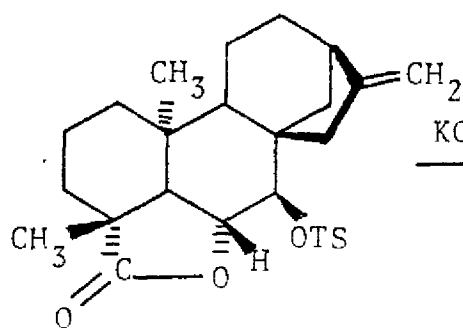
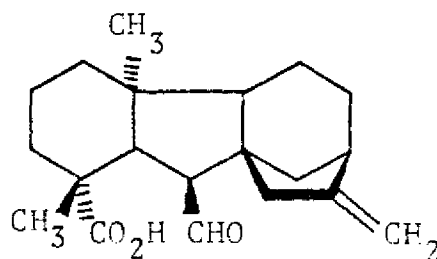
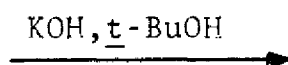
212223

+

24

2-3%

8-12%

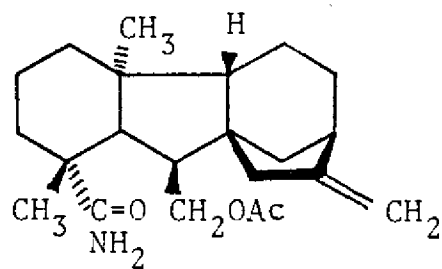
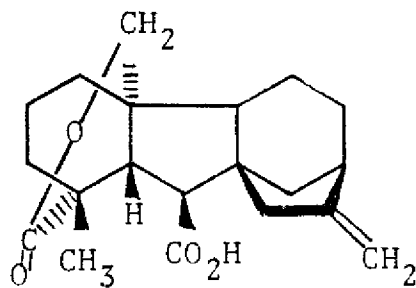
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## Scheme II (cont.)

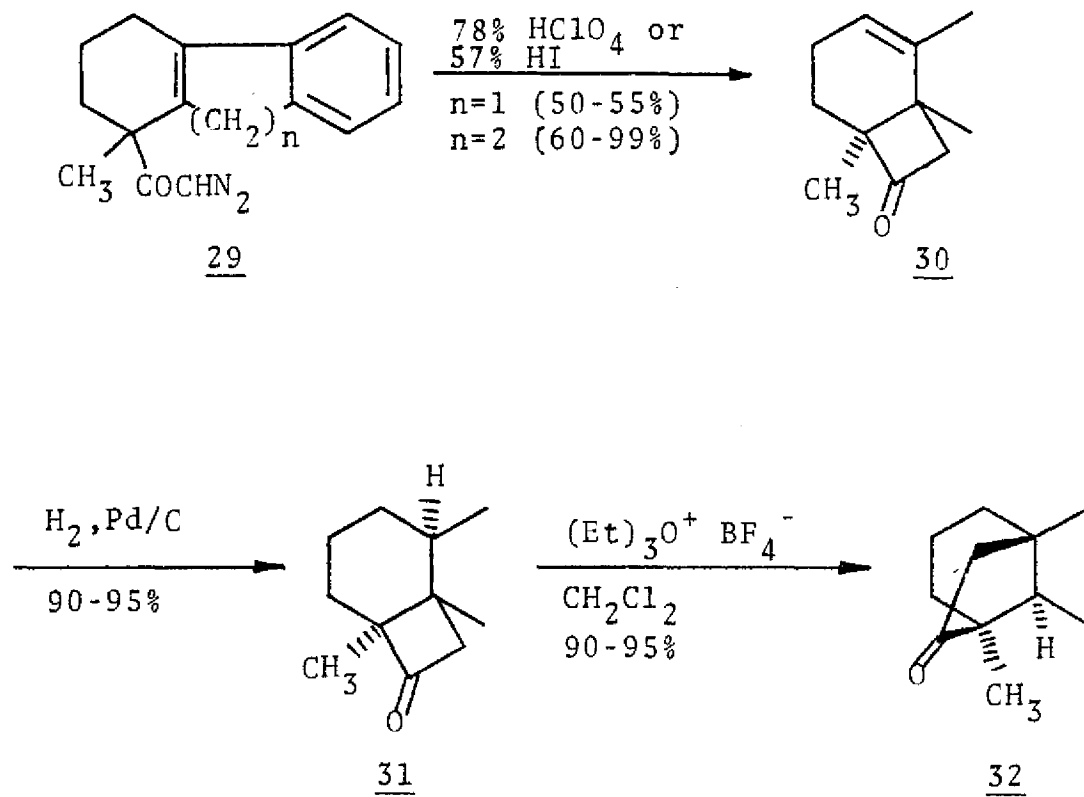
1)  $\text{NaBH}_4$ 2)  $\text{OsO}_4, \text{NaIO}_4$ 

3) Acetylate

4) Form amide

271)  $\text{Pb}(\text{OAc})_4, \text{I}_2$  $h\nu$ 2)  $\text{H}_2\text{CrO}_4$ 28

## Scheme III

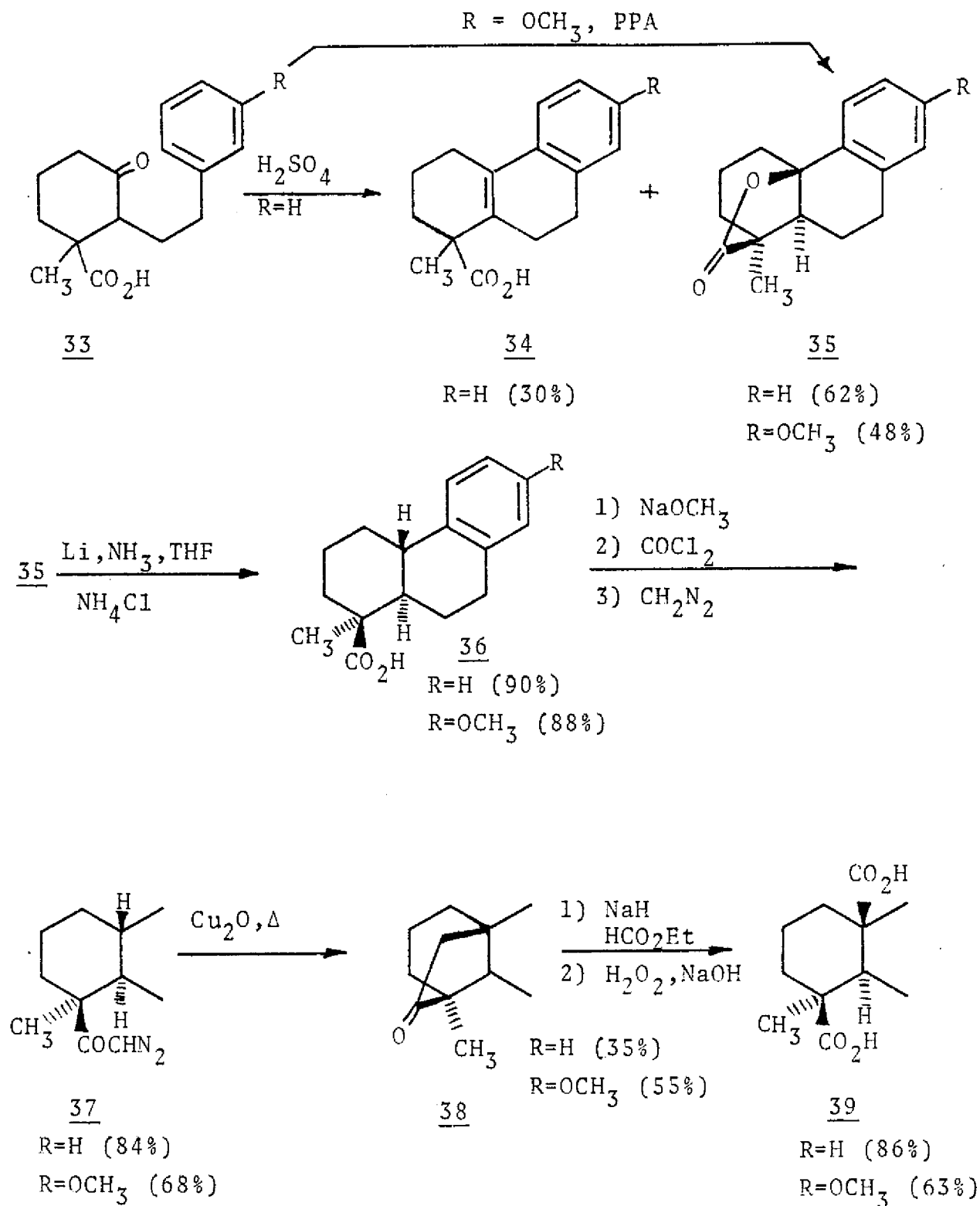


unsaturated diazoketones 29 by acid catalyzed cyclization. Catalytic hydrogenation went stereospecifically to give 31. The cyclobutanones 31 rearranged to the cyclopentanones 32 upon treatment with triethyloxonium tetrafluoroborate. Later studies<sup>12</sup> (see below) led to methods of converting the cyclic ketones to dicarboxylic acids.

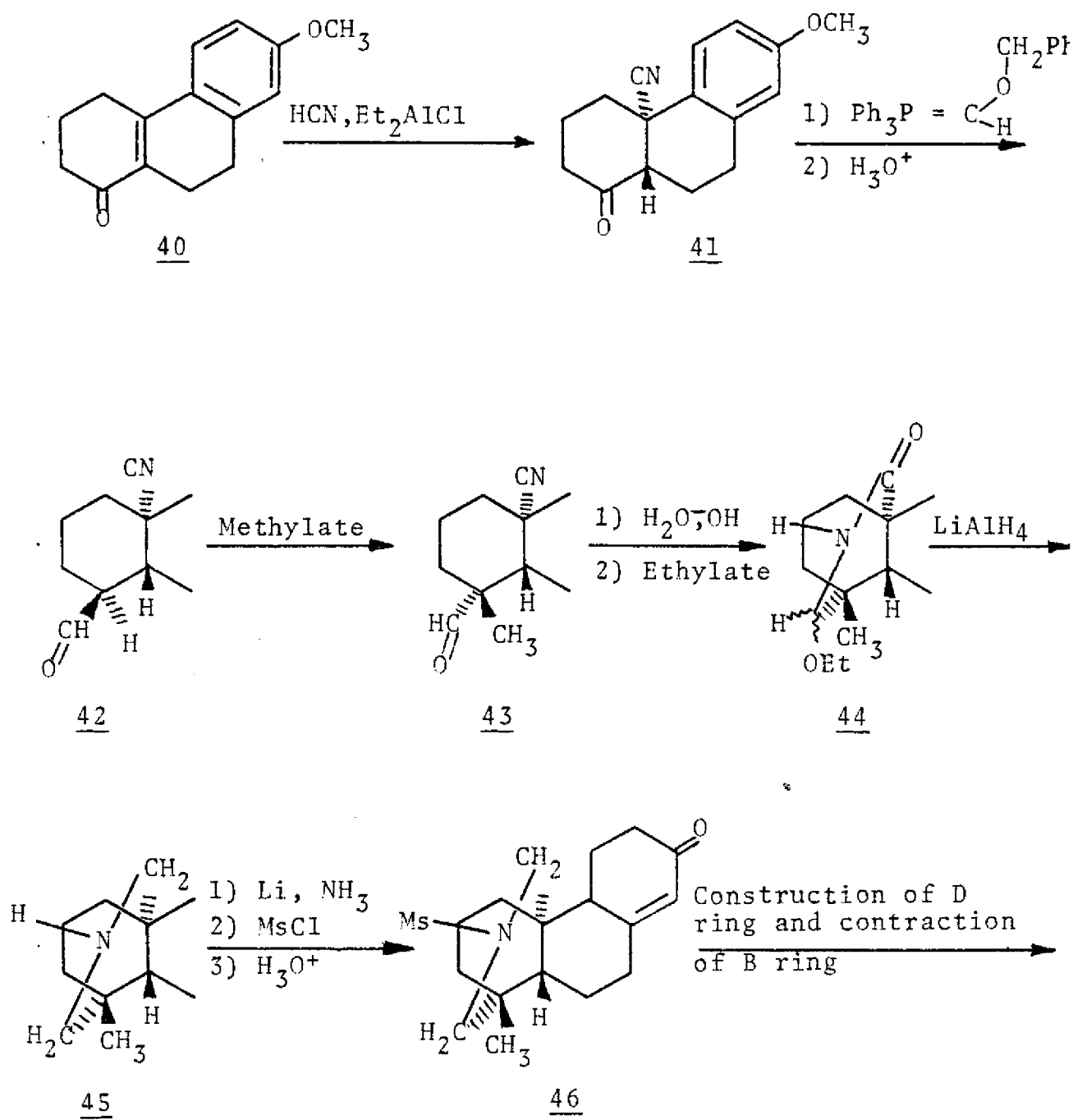
The third approach of Ghatak<sup>12</sup> (scheme IV) involved acid catalyzed cyclization of the ketoacid 33 to a mixture of the tricyclic acid 34 and the lactone 35. Subsequent reduction of the lactone 35 to the acid 36, and formation and decomposition of the diazoketone 37 gave the cyclopentanone 38. The cyclopentanone 38 could be oxidized to the dicarboxylic acid 39 by way of an intermediate formyl derivative.

For their total synthesis of gibberellin A<sub>15</sub>(10)<sup>13</sup> (scheme V), Nagata and coworkers started with the tricyclic ketone 46 which had been used previously in a synthesis of the natural product atisine.<sup>14</sup> Compound 46 was prepared from the aromatic ketone 40. Addition of HCN to the aromatic ketone 40 introduced C-20 of the final product (10) as a nitrile group. A Wittig reaction on the ketonitrile 41 using a protected aldehyde gave the aldehyde 42. A stereospecific methylation then gave compound 43, which contains the correct stereochemistry in the A ring. Compound 43 was then further transformed as shown in the scheme to give the cyclic amine 46. The conversion of the amine 46 to 47, which contains the basic gibberellin framework, involved

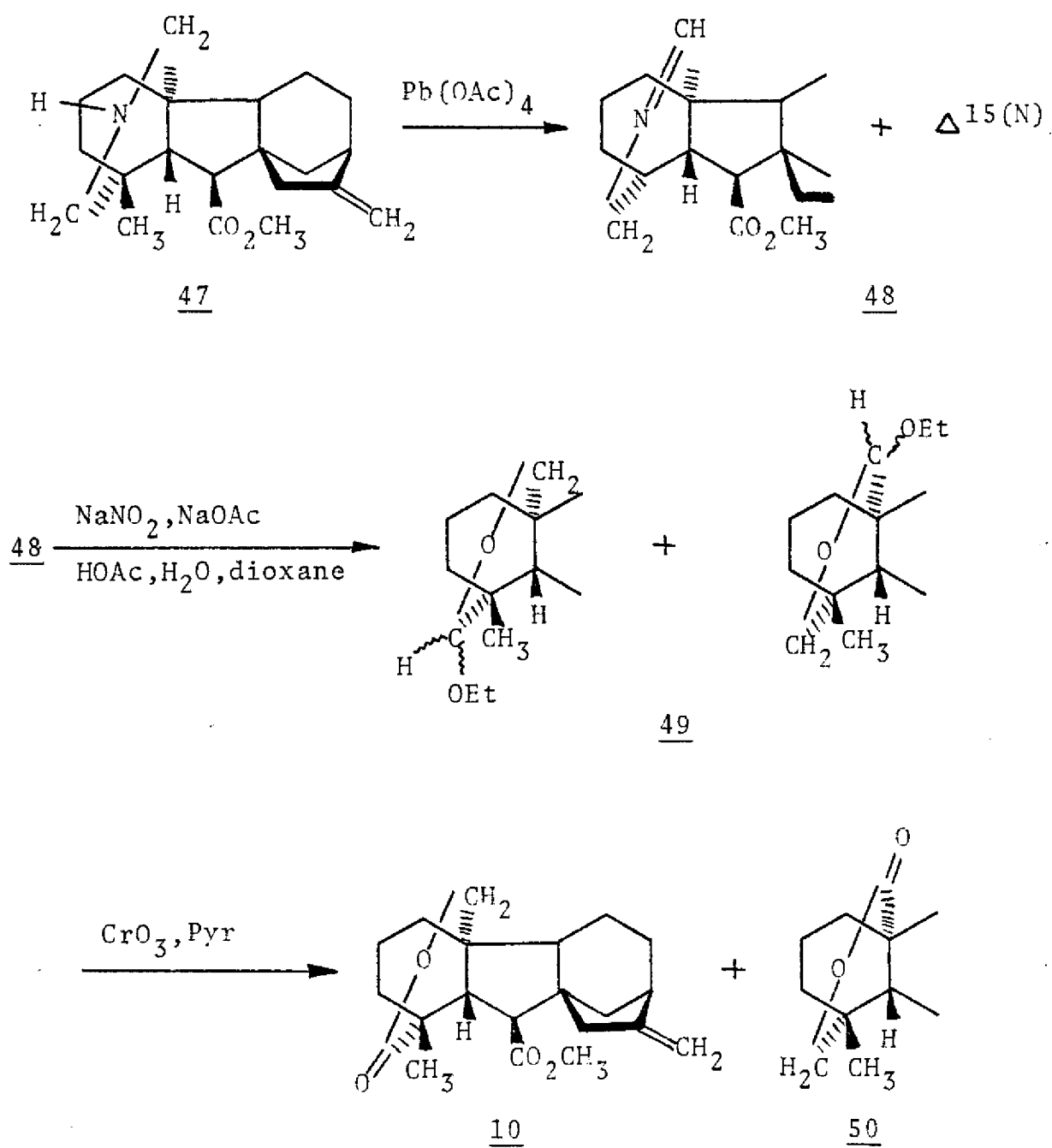
## Scheme IV



## Scheme V



## Scheme V (cont.)

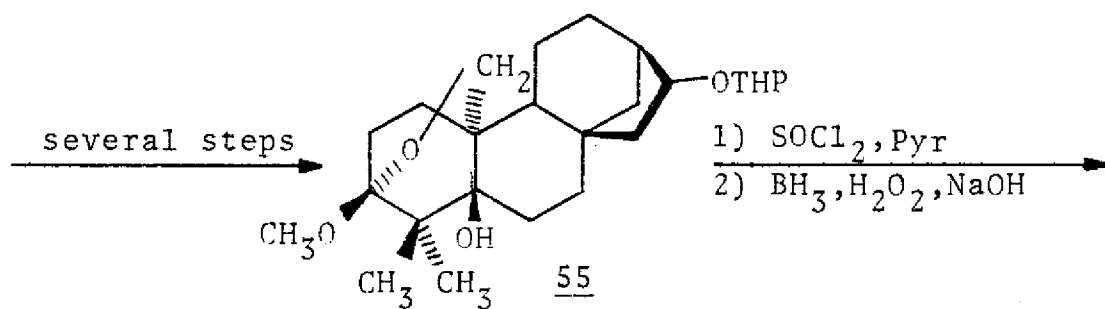
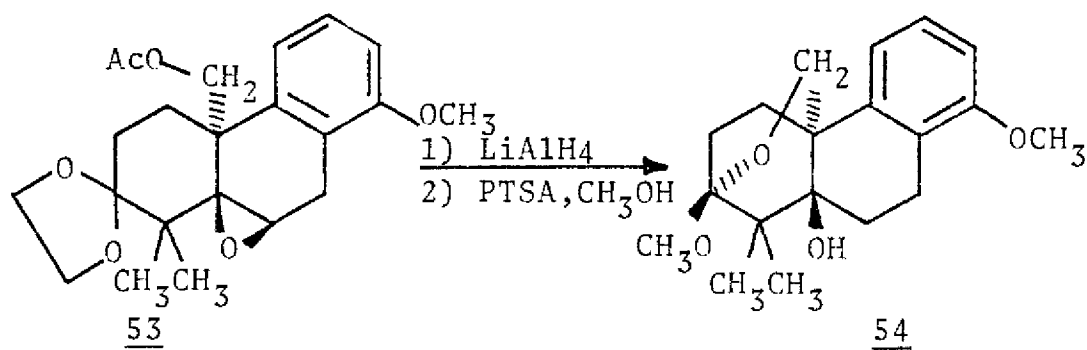
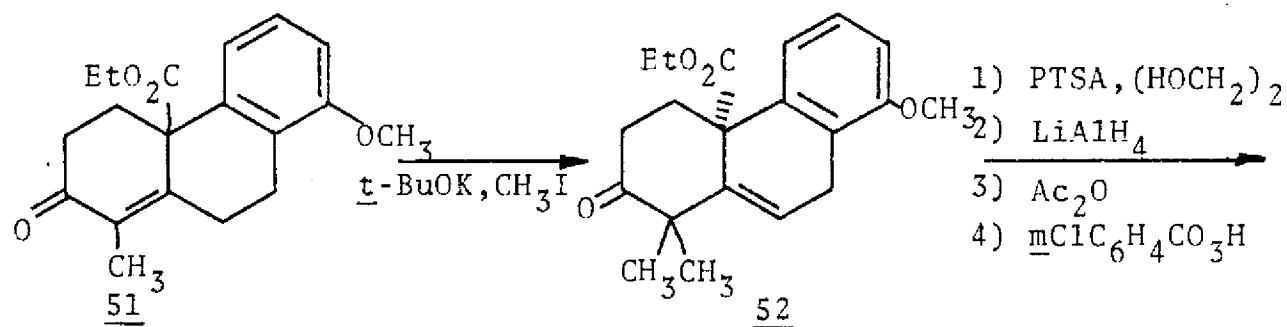


construction of the D ring and contraction of the B ring in a lengthy sequence. In order to convert the cyclic amine in 47 to the required lactone, it was first oxidized with  $\text{Pb}(\text{OAc})_4$  to a mixture of imines 48, which were then hydrolyzed by way of a nitroso intermediate to a mixture of ketals 49. Oxidation with Collin's reagent then gave the desired lactone, gibberellin  $\text{A}_{15}$  (10), as well as the isomeric lactone 50.

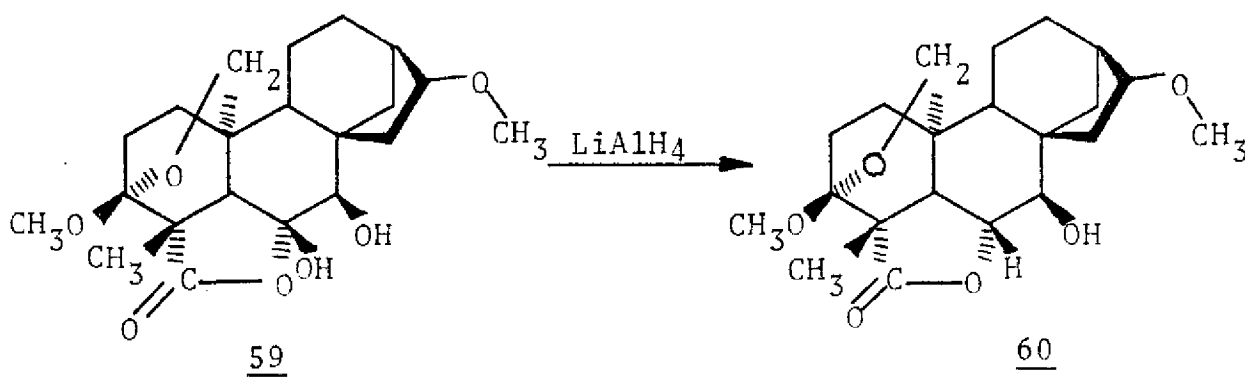
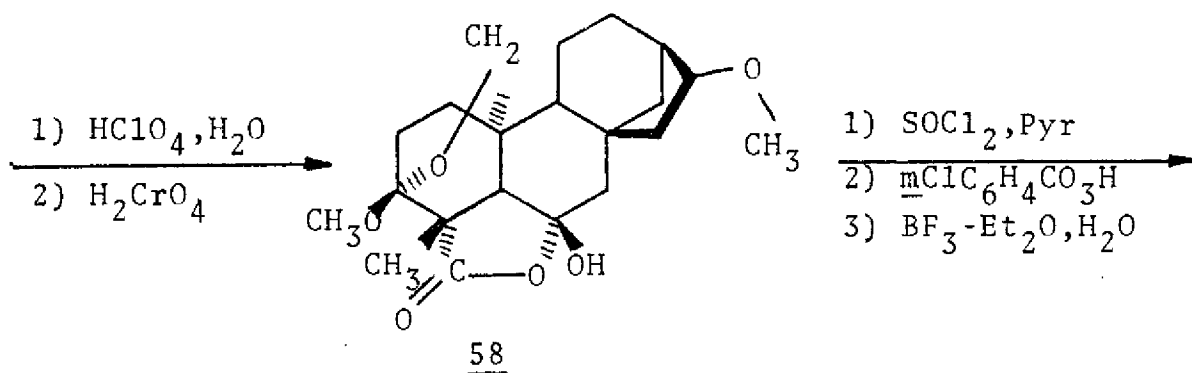
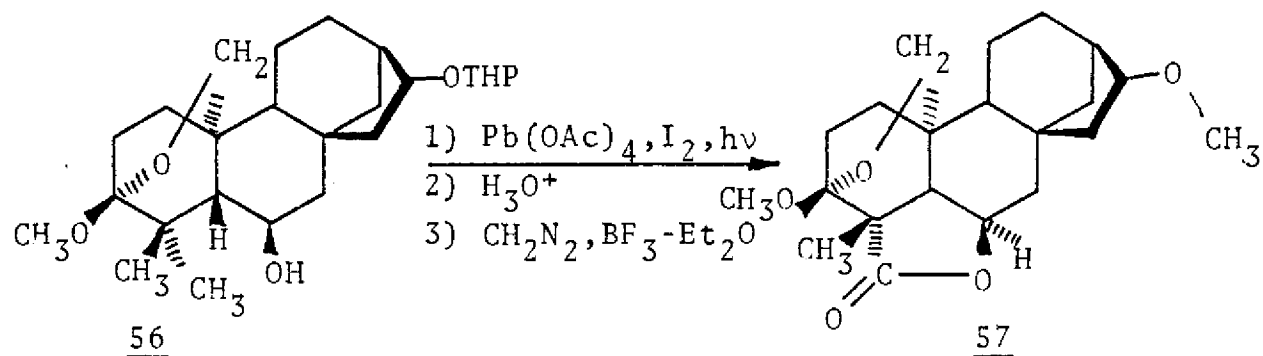
The total synthesis of gibberellin  $\text{A}_{37}$  methyl ester (64) (scheme VI) by Fujita and coworkers<sup>15</sup> used the intermediate 56 which had been prepared previously in a synthesis of the natural product enmein.<sup>16</sup> Starting with the tricyclic keto ester 51, which already contained the angular carbon unit, and which provided functionality for the C-3 hydroxyl group in compound 64, the hydroxy ketal 54 was prepared as outlined in scheme VI. The aromatic ring was then transformed into the protected C and D rings to give 55. Compound 55, by a dehydration and hydroboration sequence, was further transformed into 56, in which the hydroxyl group is oriented to allow functionalization of the  $\alpha$  methyl group. Oxidation of the hydroxy ketal 56 with  $\text{Pb}(\text{OAc})_4$  and  $\text{I}_2$  gave the lactone 57, which was then transformed into the mesylate 61 as shown in the scheme. Reaction with KOH in *t*-BuOH induced contraction of the B ring to give the aldehyde 62. Aldehyde 62 was then converted to the gibberellin methyl ester 64 by the series of reactions outlined in the scheme.



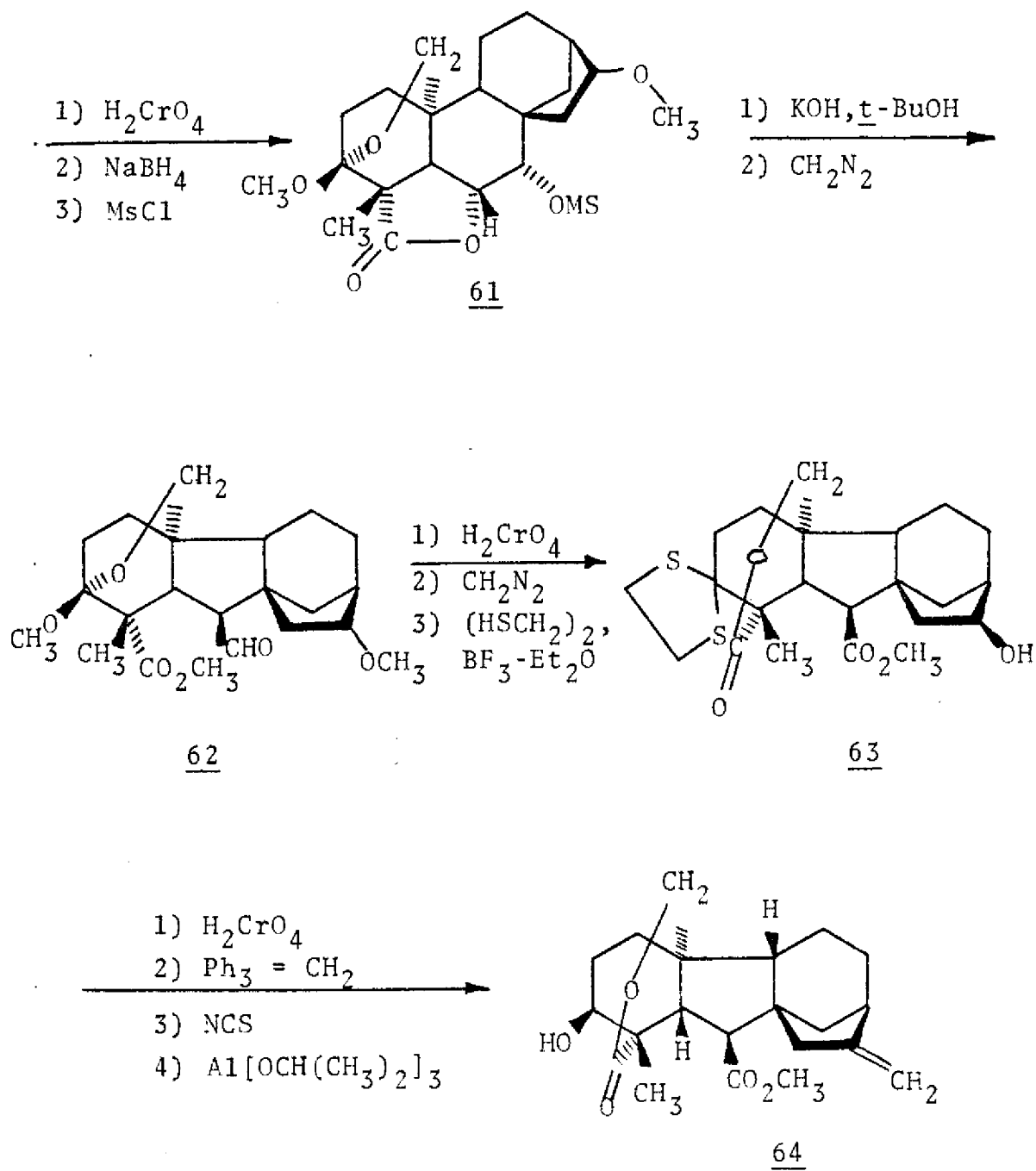
Scheme VI



## Scheme VI (cont.)



## Scheme VI (cont.)

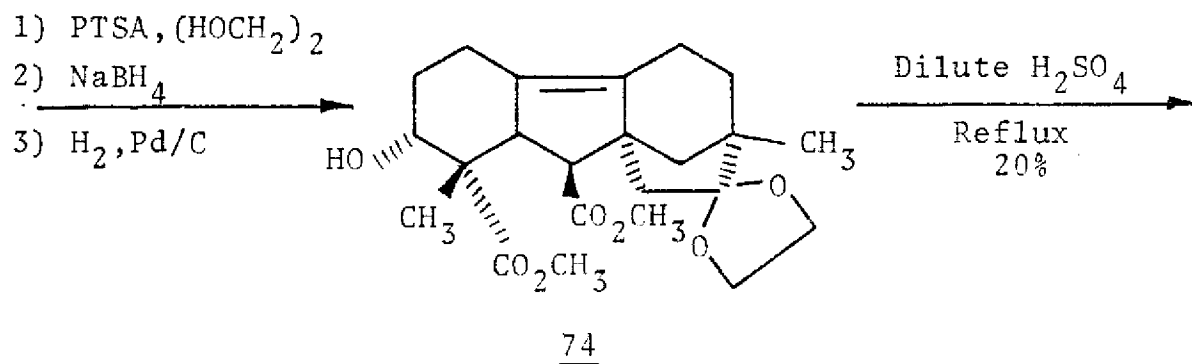
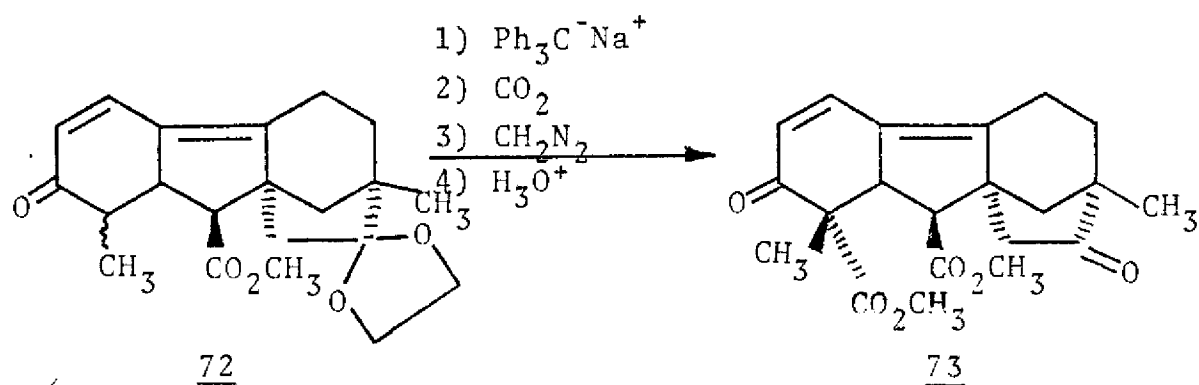
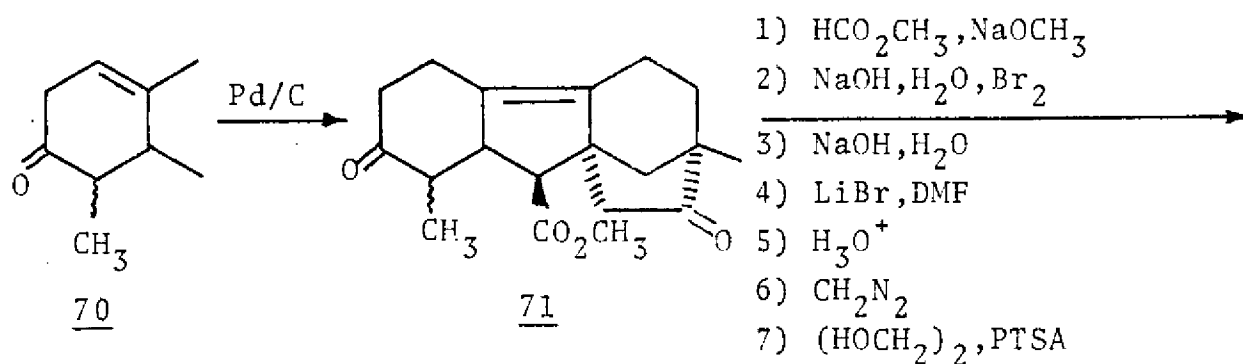


### C<sub>19</sub> Gibberellins

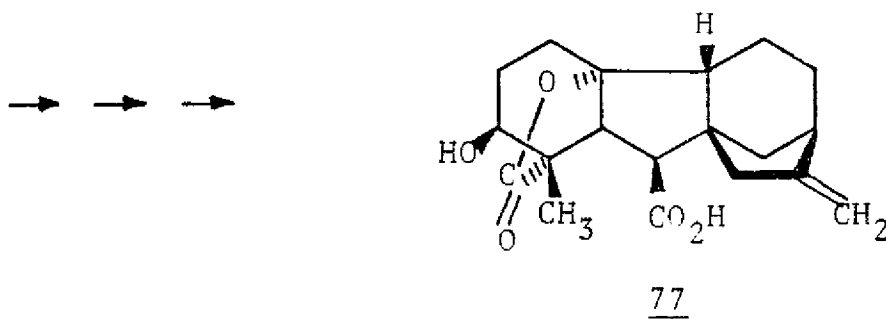
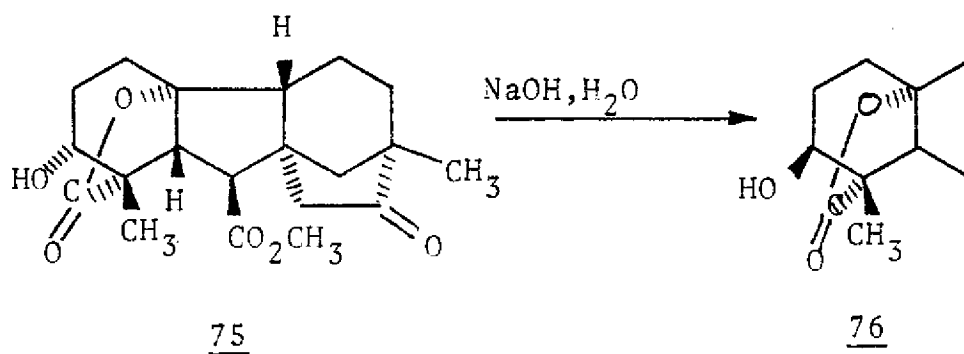
One of the first syntheses of the A ring lactone system found in some C<sub>19</sub> gibberellins was that of Mori and coworkers, who completed a formal total synthesis of gibberellin A<sub>4</sub>(77).<sup>17</sup> Eppigibberic acid (65) (scheme VII) was prepared in 21 steps from o-xylene. The aromatic ring of 65 was functionalized with HNO<sub>3</sub> in Ac<sub>2</sub>O and then converted to the phenol 68. Catalytic reduction of the aromatic ring of 68 followed by oxidation of the resulting mixture of alcohols then gave the ketone 69 in 4% isolated yield from 68. Ketone 69 was transformed into the more stable  $\beta,\gamma$  isomer of enone 70 by a sequence of reactions in which the main step was bromination of a formyl derivative. Without activation, ketone 69 was brominated preferentially in the C1 position. After isomerization of the double bond, the sequence of reactions was repeated, and the resulting diketone was selectively ketalized to give the dienone 72. The diester 73 was obtained in 11% yield by carbomethoxylation of dienone 72. According to the authors, this last reaction introduced the carbomethoxy group stereospecifically, although a complex mixture of products was formed as well. After selective ketalization, 73 was reduced to the alcohol 74, which was lactonized in refluxing dilute H<sub>2</sub>SO<sub>4</sub> to give the lactone 75 in 20% yield. The synthesis of lactone 75, together with some earlier studies on the base catalyzed reversible epimerization of 75 (yields a small amount of the axial



## Scheme VII (cont.)



## Scheme VII (cont.)



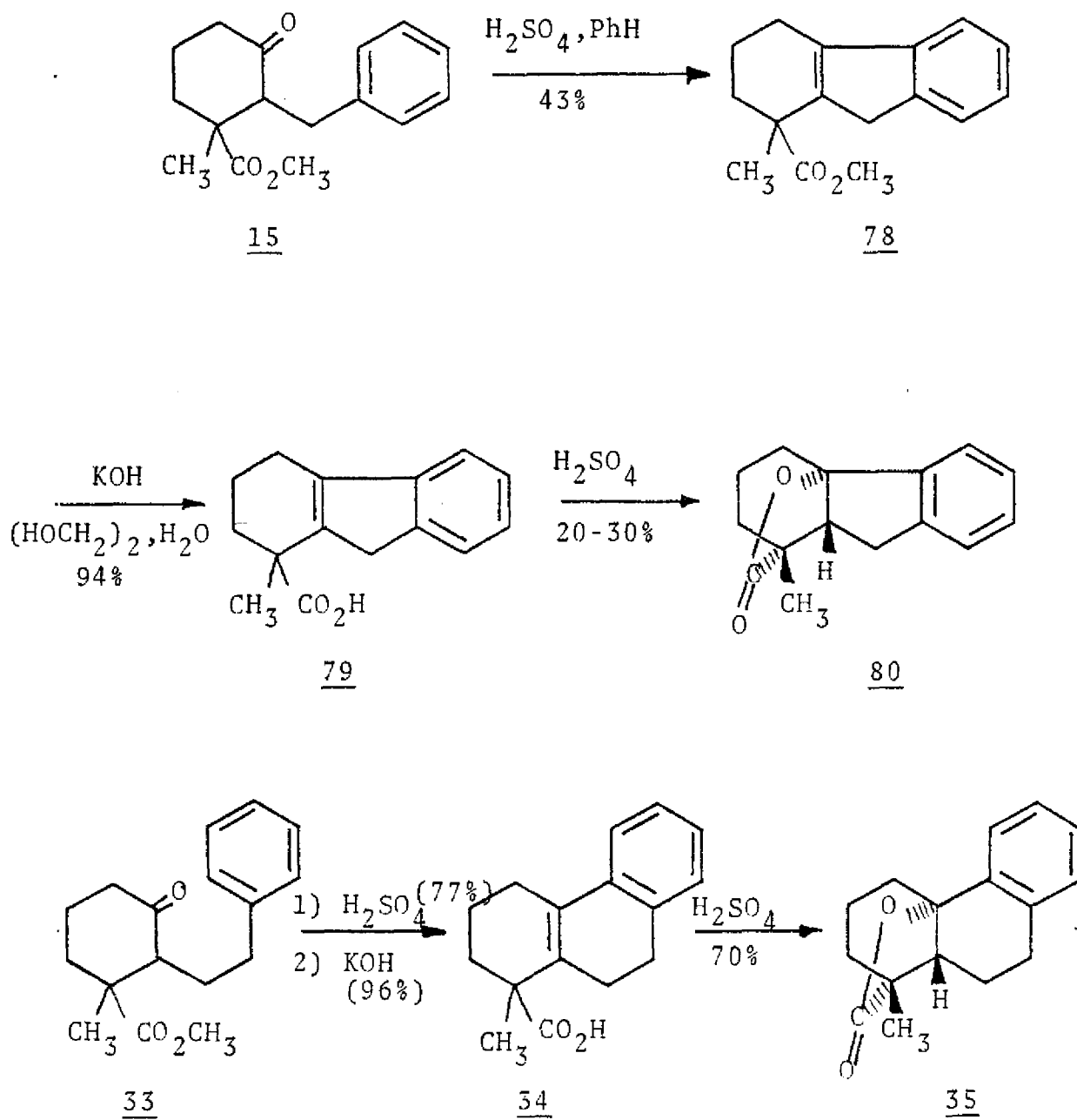
alcohol 76<sup>18</sup>) and the isomerization of the C and D rings,<sup>19</sup> constitute a formal total synthesis of gibberellin A<sub>4</sub>(77).

An intermediate that was used by Ghatak to study the synthesis of C<sub>20</sub> gibberellins (see scheme II) was also used as a model compound for the synthesis of C<sub>19</sub> gibberellins.<sup>20</sup> Acid catalyzed cyclization of the aromatic ketone 15 (scheme VIII) and subsequent base hydrolysis gave the unsaturated acid 79. This compound lactonized with concentrated H<sub>2</sub>SO<sub>4</sub> to give the lactone 80 in 20-30% yield. The analogous unsaturated acid 34 under similar conditions gave the lactone 35 in 70% yield.<sup>21</sup> The higher yield in the latter case is attributed to differences in ring strain.

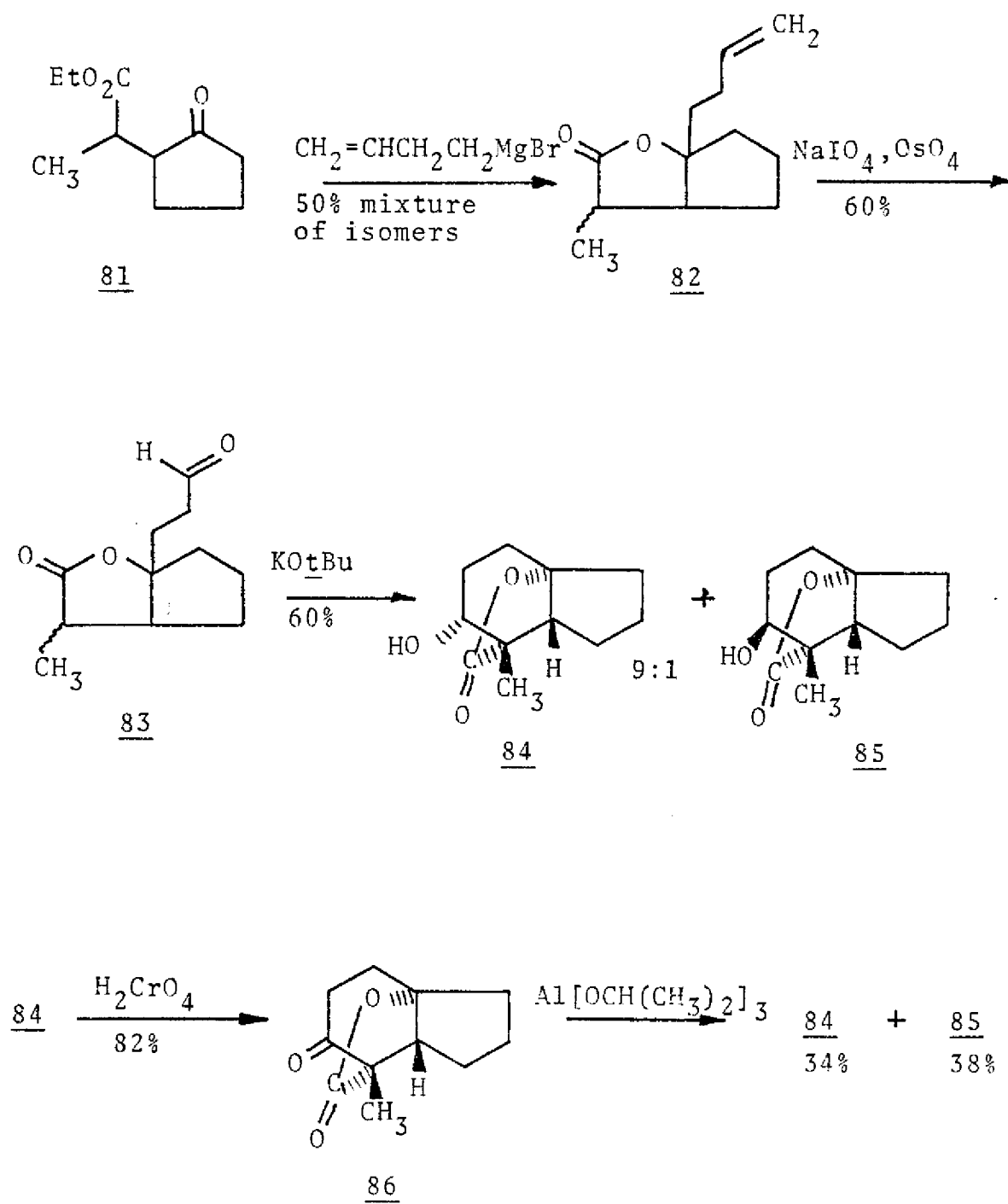
Dolby and coworkers have reported an approach to the A ring lactone system in which the lactone portion is completed first.<sup>22</sup> Grignard addition to the keto ester 81 (scheme IX) followed by oxidative cleavage of the resulting olefin gave the aldehyde 83. Base catalyzed intramolecular aldol condensation of aldehyde 83 gave a mixture of the equatorial alcohol 84 and the axial alcohol 85, with the equatorial alcohol predominating substantially. However, 84 could be oxidized to the keto ester 86, which could then be reduced with aluminum isopropoxide to give the axial alcohol 85 as the major product. In a similar manner, the aldehyde 89, derived from the keto ester 81 as shown in the scheme, was cyclized to the unsaturated alcohol 90. Subsequent oxidation and reduction gave the desired axial alcohol 92.



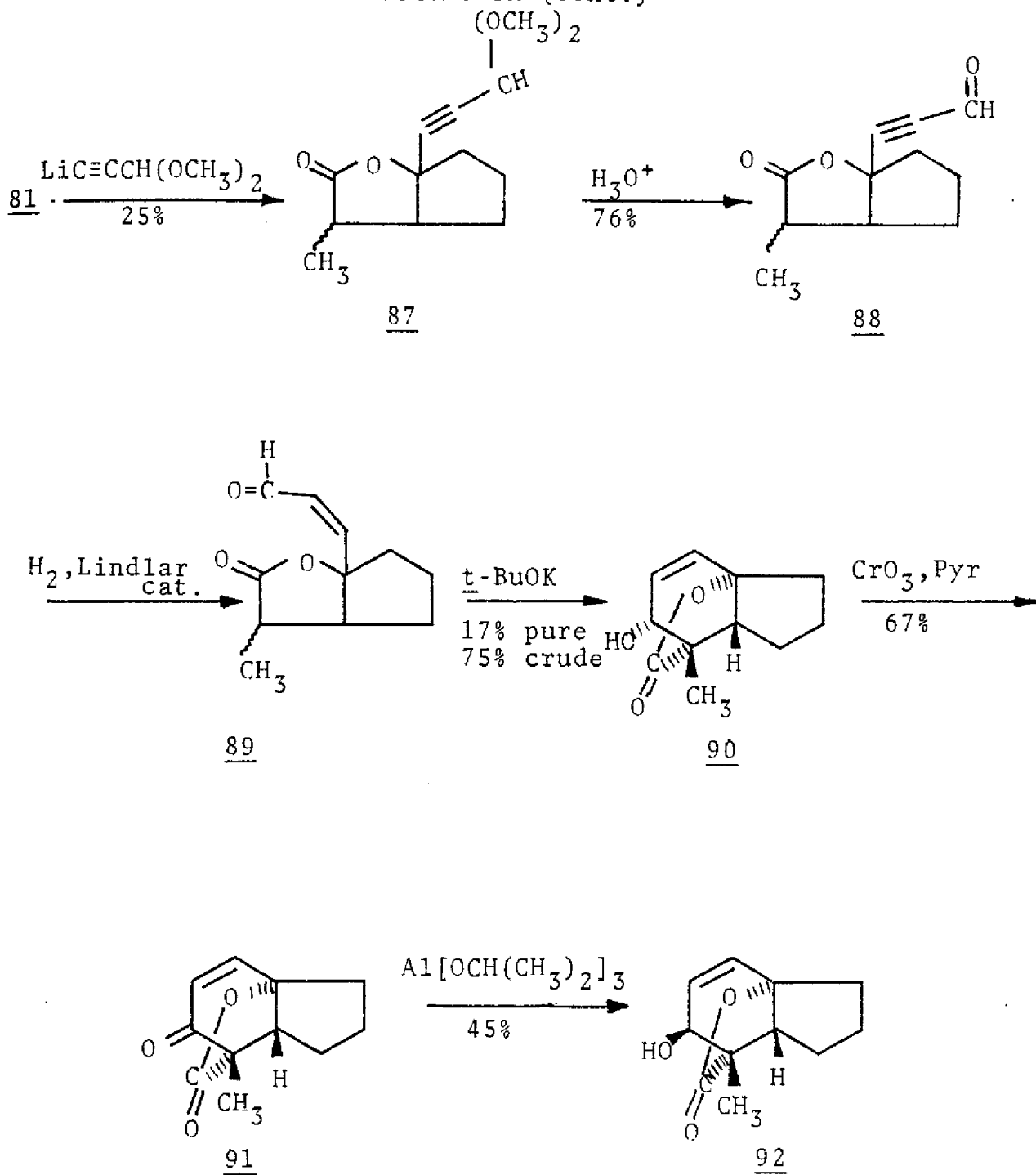
## Scheme VIII



## Scheme IX



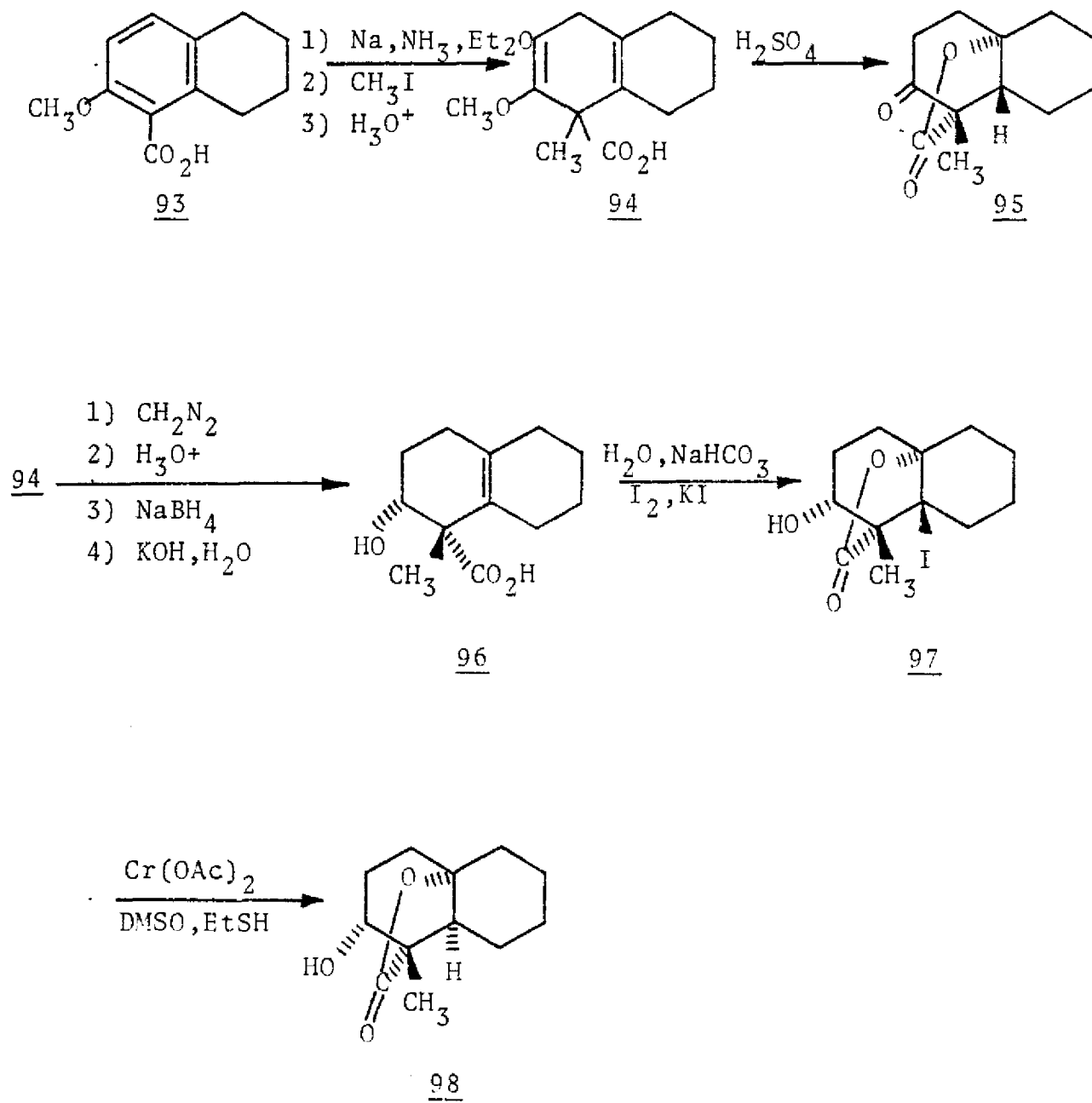
## Scheme IX (cont.)



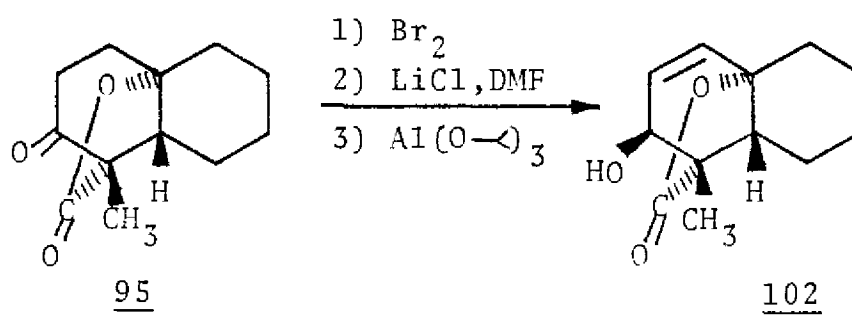
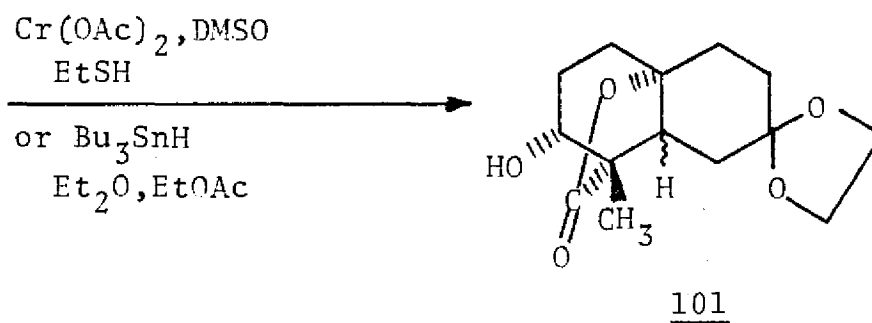
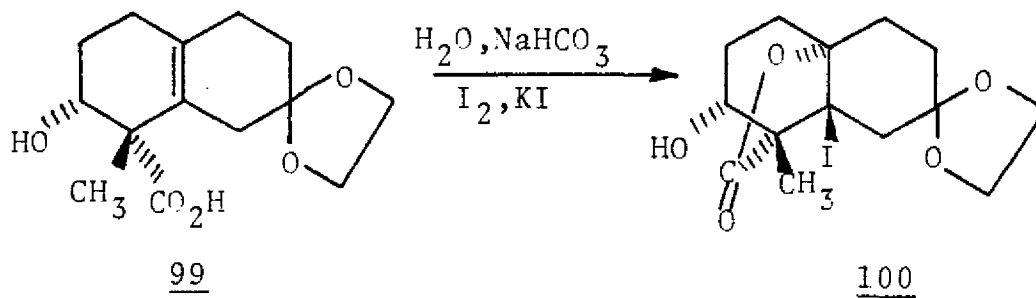
Lowenthal and coworkers have shown that functionalized aromatic rings can serve as A ring precursors.<sup>23</sup> Reduction of the aromatic acid 93 (scheme X) with sodium in ammonia followed by methylation of the intermediate enolate anion with methyl iodide gave the dihydro acid 94. This compound could be transformed to the ketolactone 95 in low yield with concentrated  $\text{H}_2\text{SO}_4$ . The dihydro acid 94 was converted to the alcohol 96 by first protecting the carboxyl group as an ester, hydrolyzing the enol ether and reducing the resulting ketone with  $\text{NaBH}_4$ , and finally hydrolyzing the methyl ester to the carboxylic acid. Lactonization of 96 with iodine in aqueous sodium bicarbonate gave the iodolactone 97. However, reduction of the iodide with  $\text{Cr}(\text{OAc})_2$ , EtSH reagent in DMSO introduced the hydrogen from the undesired  $\alpha$  side. The alcohol 99 was prepared in a similar manner and converted to the iodolactone 100. Reduction of the iodide with both  $\text{Cr}(\text{OAc})_2$ , EtSH reagent and  $\text{Bu}_3\text{SnH}$  gave an inseparable mixture of products. The keto lactone 95 was further transformed into the allylic alcohol system 102 found in gibberellic acid with a bromination, dehydrobromination sequence to give the conjugated ketone, followed by reduction to the alcohol with aluminum isopropoxide.

Lowenthal has also reported a synthesis of the intermediate 108<sup>24a</sup> (scheme XI) and the conversion of this compound to the intermediates 111 and 112.<sup>24b</sup> These latter two compound could serve to eventually give natural

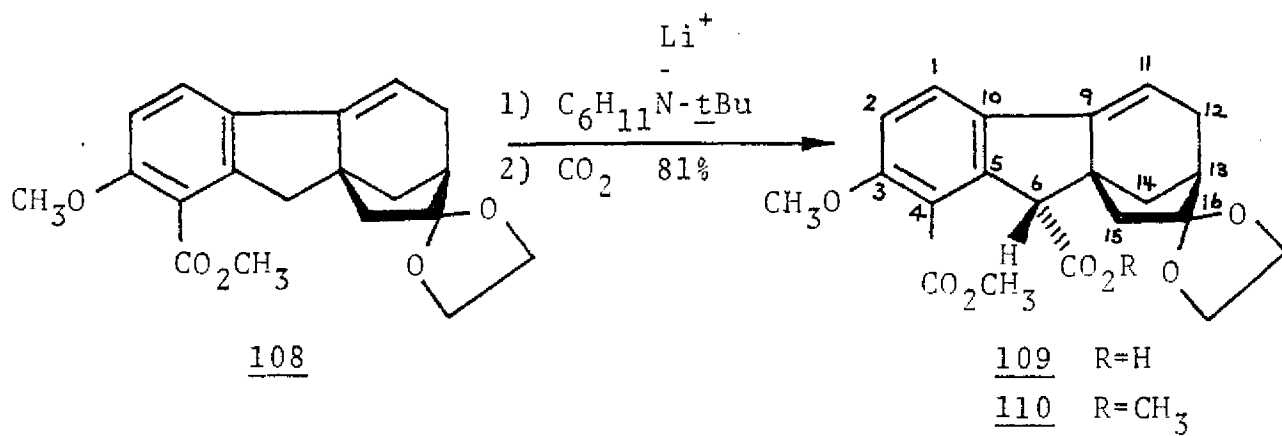
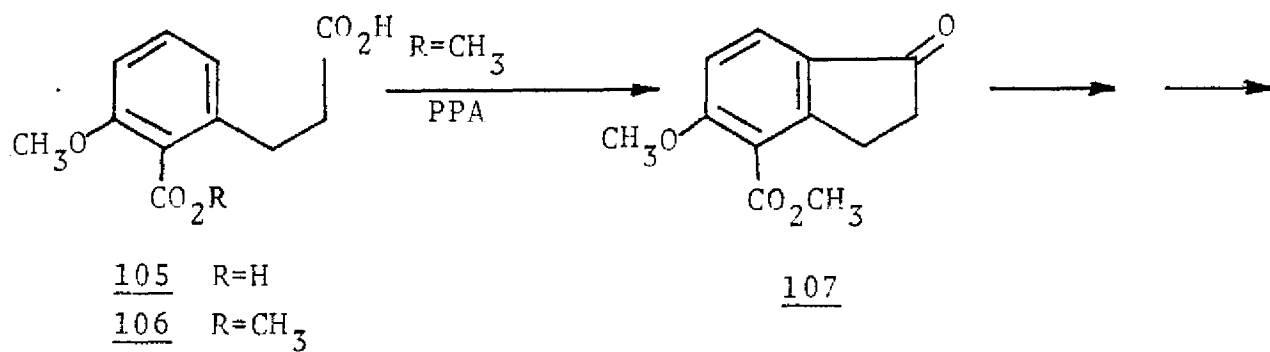
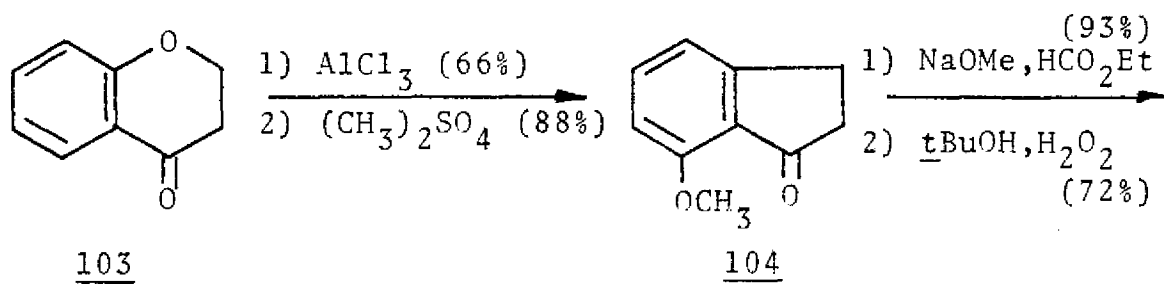
Scheme X



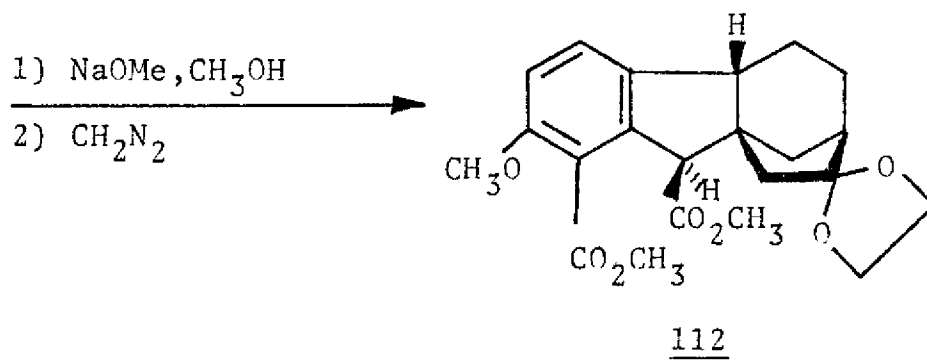
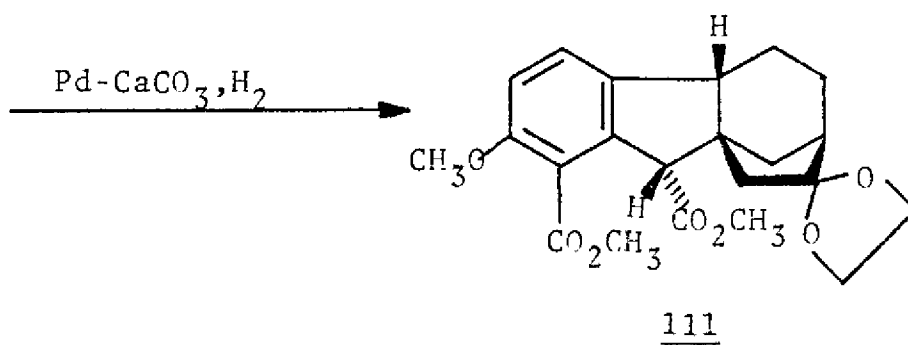
## Scheme X (cont.)



## Scheme XI



## Scheme XI (cont.)

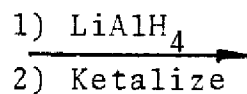
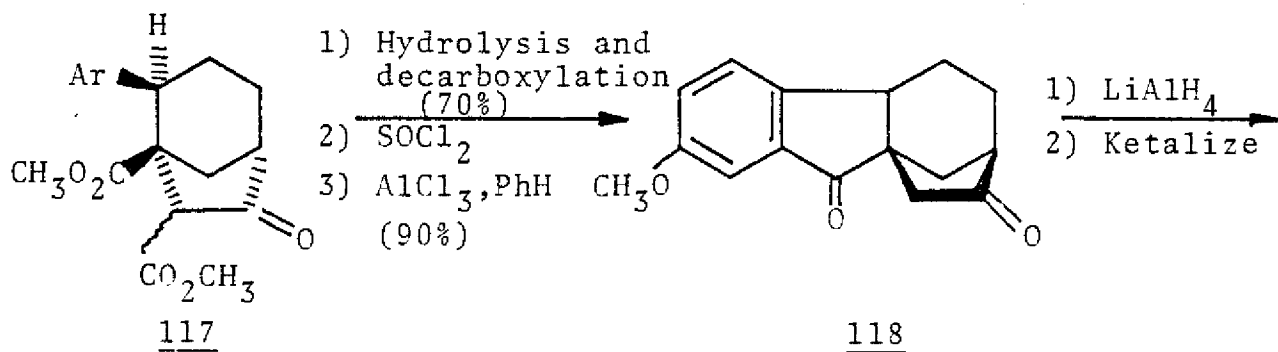
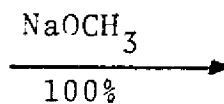
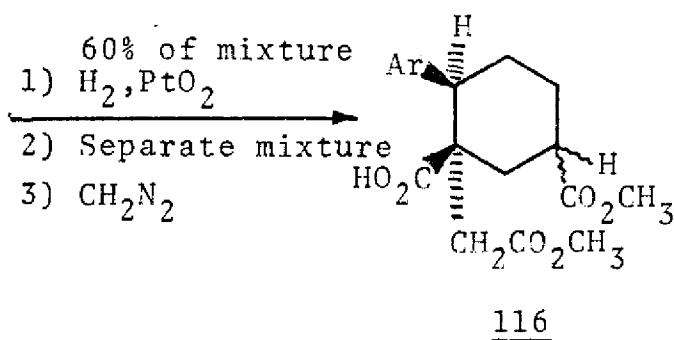
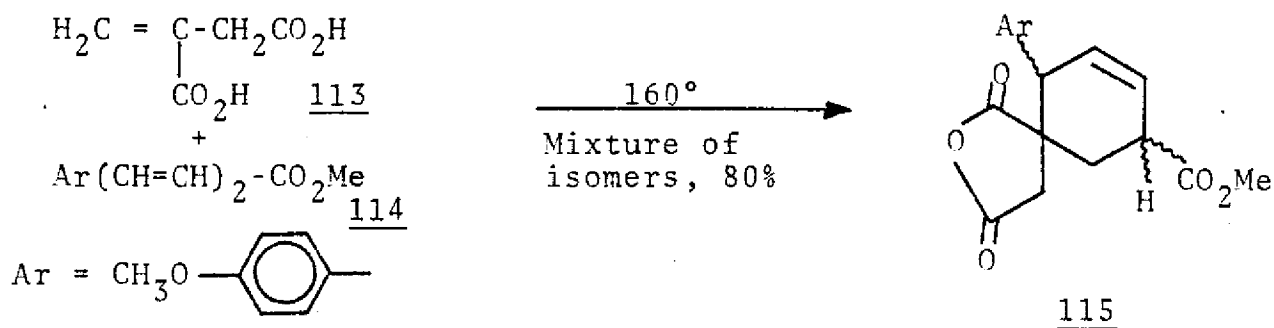




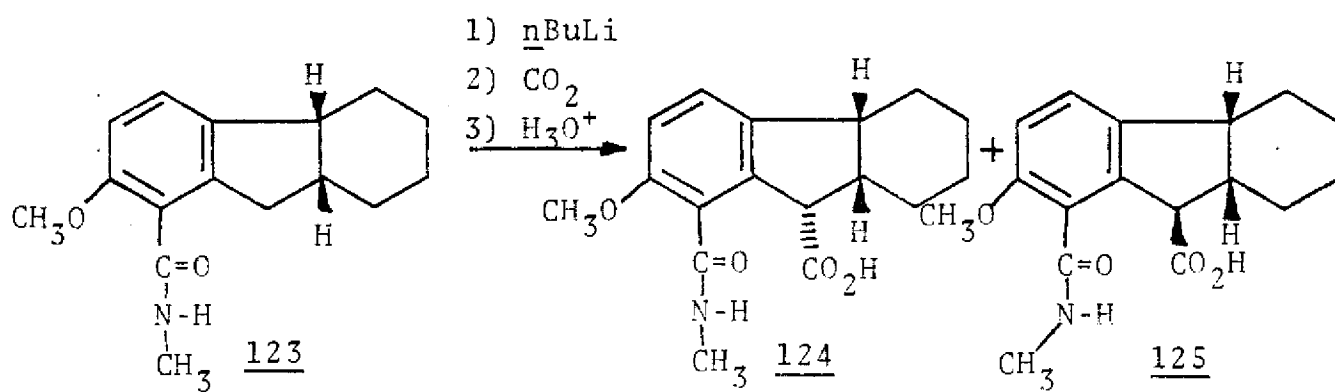
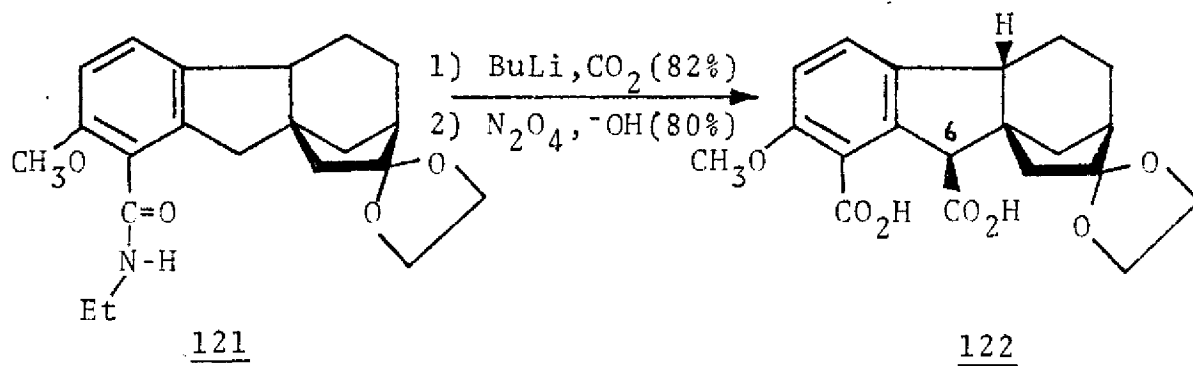
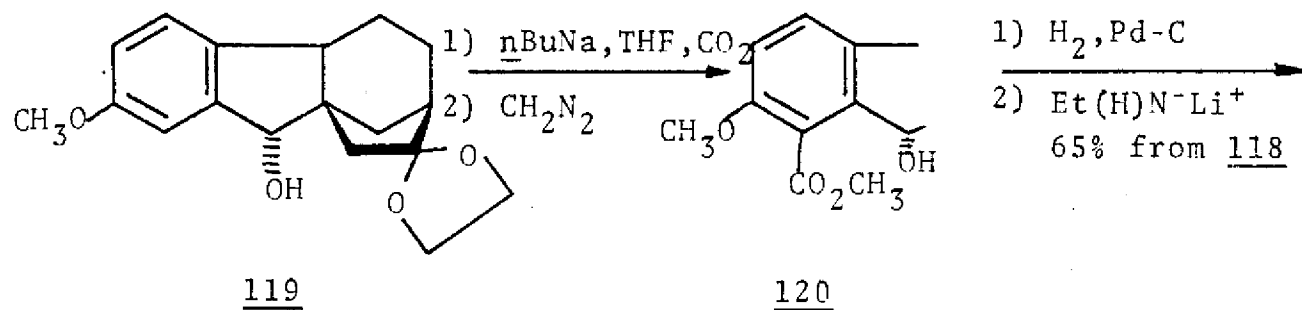
gibberellins after application of the reduction, methylation sequence described above. The key intermediate which contained the properly functionalized aromatic ring was the keto ester 107. This compound was prepared starting from chroman-4-one (103). Aluminum chloride catalyzed C-O bond cleavage and Friedel-Crafts cyclization gave 7-hydroxy indan-1-one, which was methylated to give 7-methoxy indan-1-one (104). After activation as a formyl derivative, the five membered ring was cleaved with  $H_2O_2$  to give the dicarboxylic acid 105. Acid catalyzed cyclization of the corresponding half ester gave the keto ester 107, which was further transformed to the unsaturated ketal 108. The C-6 carboxyl group was introduced by a metalation reaction employing a nonnucleophilic mixed amide base to give the diester 110 after carboxylation and esterification. Hydrogenation of this compound then gave the gibberellin intermediate 111 which had the C-6 carboxyl in the less stable  $\alpha$  position. Base catalyzed epimerization gave 112.

Earlier, Baker and Goudie had reported the preparation of diacid 122 (scheme XII)<sup>25</sup> which corresponds to diester 112 prepared by Lowenthal.<sup>24b</sup> The gibbane skeleton of diketone 118 was achieved beginning with a Diels-Alder condensation of 113 and 114 to give a mixture of the isomeric anhydrides 115, part of which was converted by catalytic hydrogenation followed by esterification to 116. Dieckman condensation gave 117, and Friedel Crafts

## Scheme XII



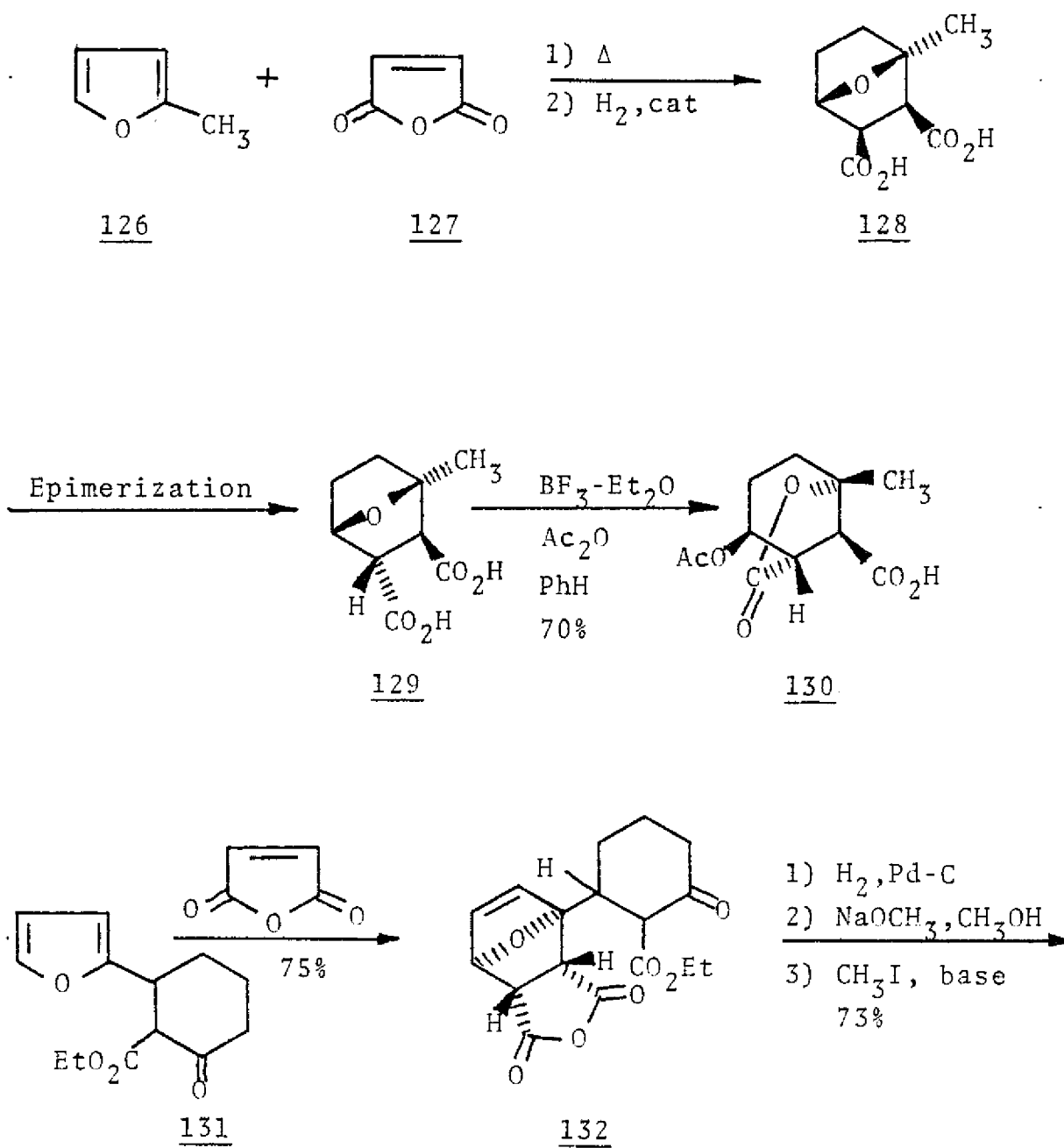
## Scheme XII (cont.)



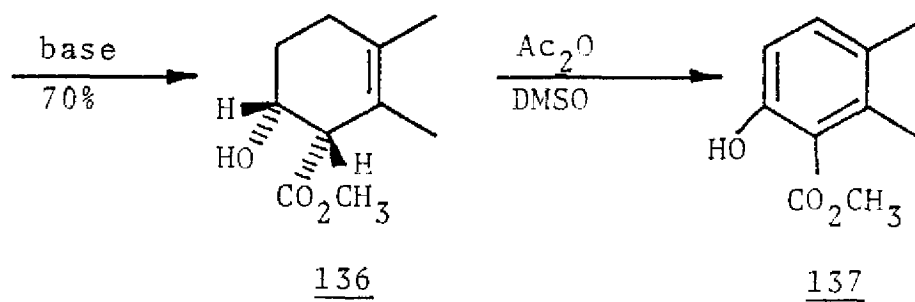
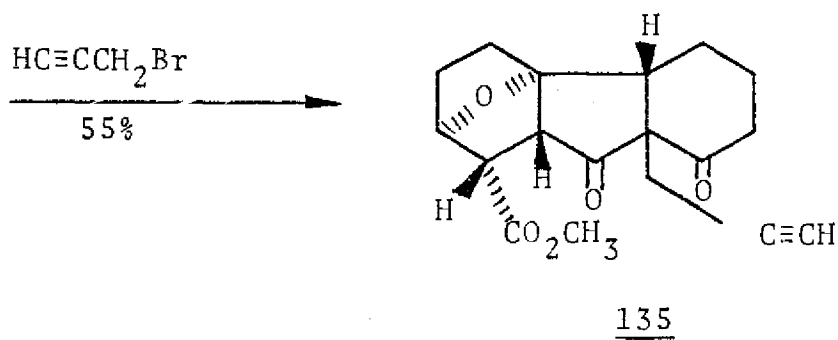
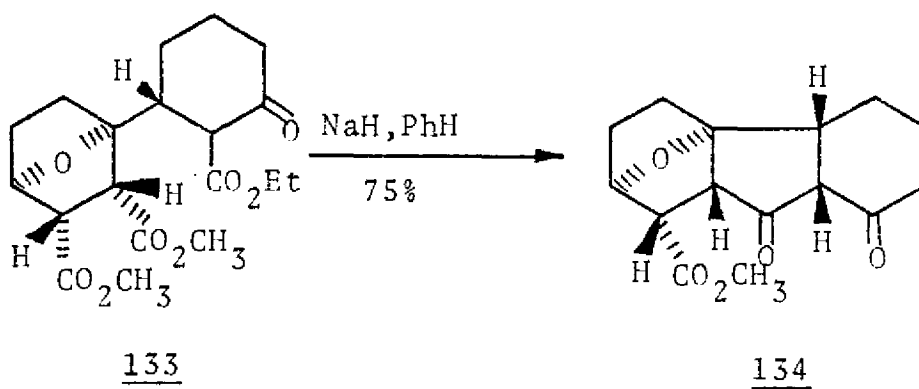
cyclization after hydrolysis and decarboxylation then gave the diketone 118.<sup>25a</sup> The carboxyl group at C-4 was introduced by the method of House, Bare, and Hanners,<sup>26</sup> for which the diketone 118 was first reduced to the alcohol, and then ketalized to give 119. A regiospecific metalation with n-BuNa and subsequent carboxylation and esterification gave the hydroxy ester 120. A directed metalation and carboxylation of the amide 121 gave an amido acid, which was hydrolyzed as a nitroso derivative to the dicarboxylic acid 122 containing the C-6 carboxyl group in the more stable  $\beta$  position.<sup>25b</sup> This regiospecific metalation was also used by House, Hanners, and Racah with the amide 123 to give the acid amides 124 and 125 in a ratio of 1.3:1.<sup>27</sup> In this case the product with the carboxyl group in the less stable configuration was predominant.

Kitahara and coworkers found that the bicyclic ether 129 (scheme XIII) could be converted with acid catalysis to the model lactone 130 in good yield.<sup>28a</sup> Ether 129 was derived from a Diels-Alder condensation between maleic anhydride (127) and 2-methyl furan (126), followed by hydrogenation and epimerization. When the same reaction was applied to a more complex system,<sup>28b</sup> apparently the proper stereochemistry for the Diels-Alder adduct 132 could not be obtained, and subsequent base cyclization of the diester 133 gave the tricyclic compound 134 having the ether linkage on the undesirable  $\alpha$  side. After alkylation with propynyl

## Scheme XIII



## Scheme XIII (cont.)

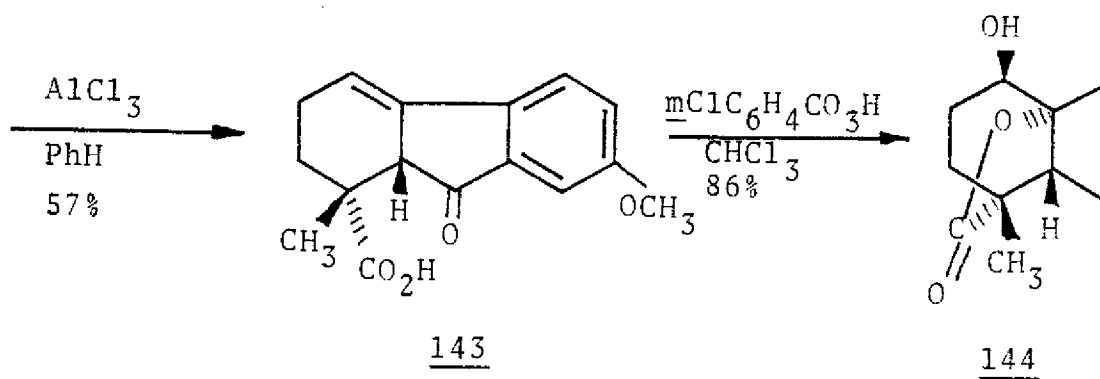
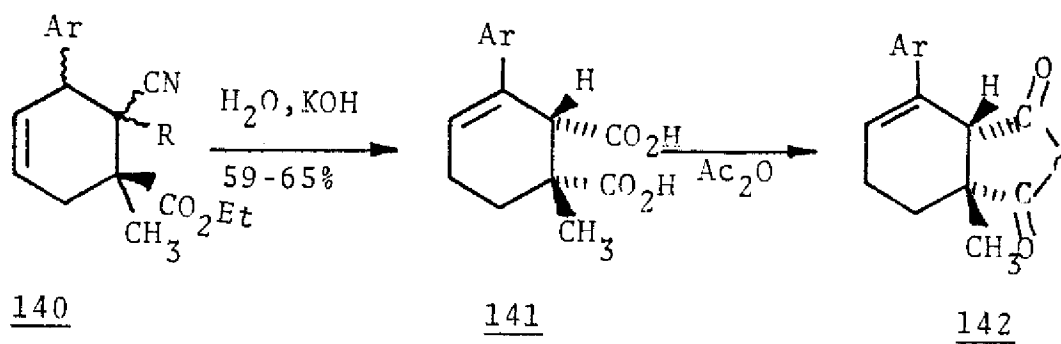
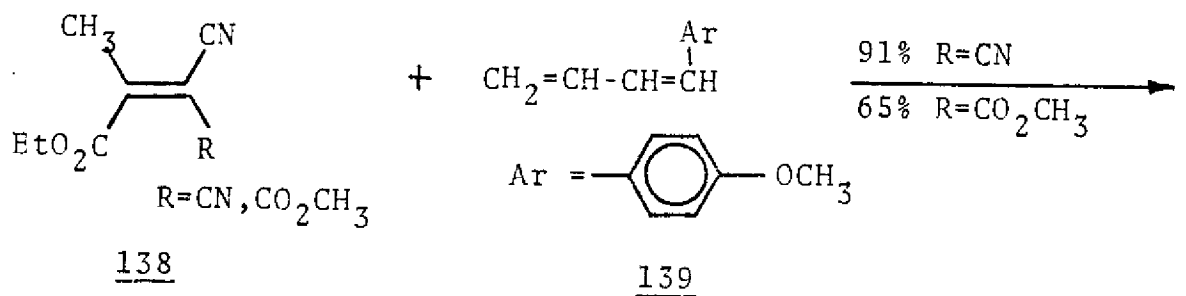


bromide, base treatment gave hydroxy ester 136, which was oxidized to the phenolic ester 137 with  $\text{Ac}_2\text{O}$  in DMSO.

Hori and Nakanishi have reported a synthesis of the gibberellin model compound 144 by the transformations outlined in scheme XIV.<sup>29</sup> The sequence of reactions begins with a Diels-Alder condensation between compounds 138 and 139, and the product was hydrolyzed to give the diacid 141. The corresponding anhydride 142 underwent  $\text{AlCl}_3$  catalyzed cyclization to the keto acid 143. The keto acid 143 upon oxidation with *m*-chloro perbenzoic acid gave the hydroxy lactone 144.

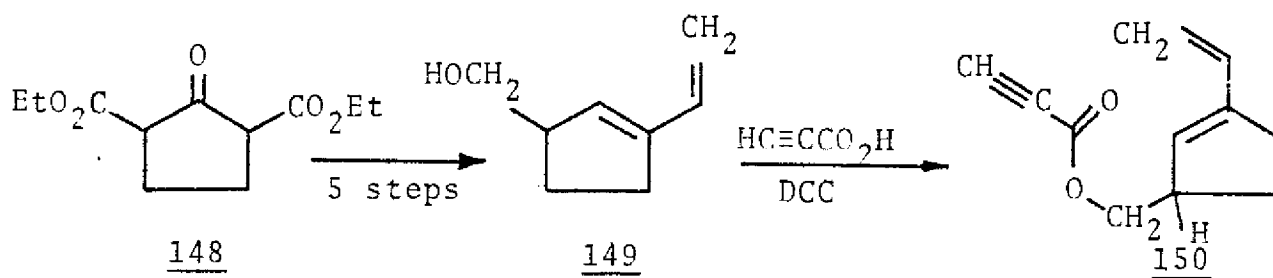
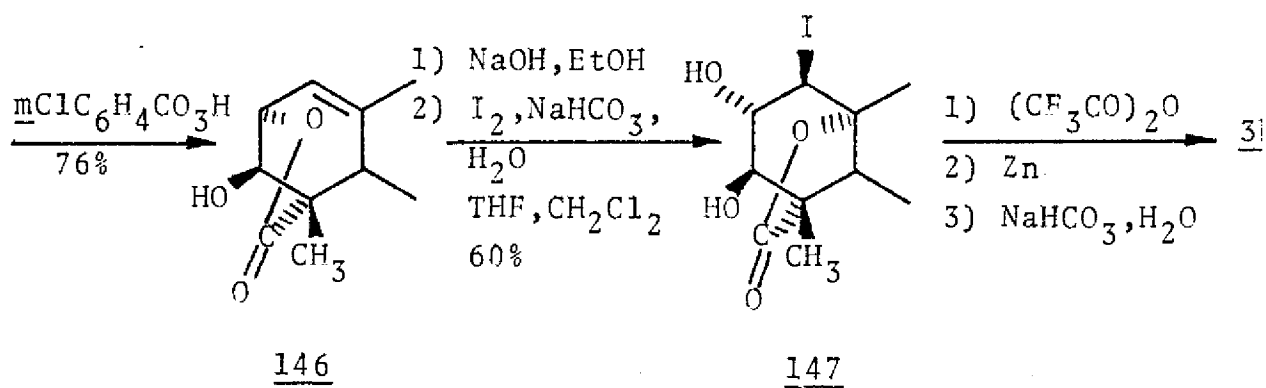
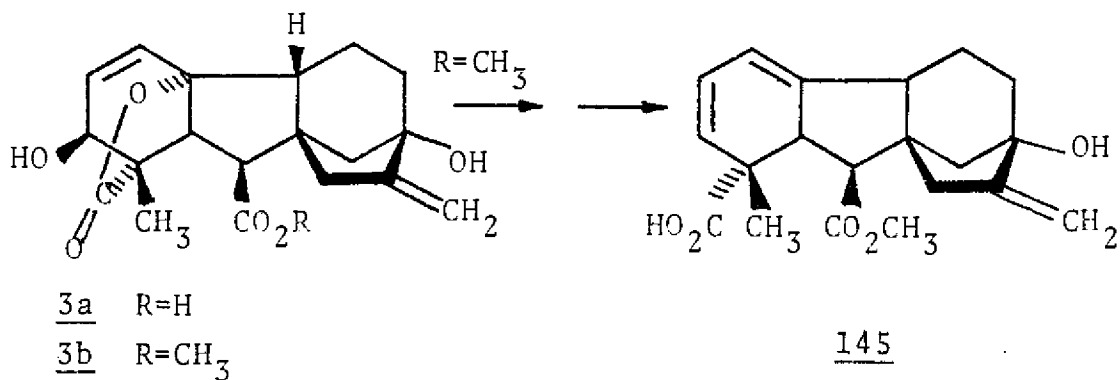
Corey and Carney have reported a route which gives the entire A ring structure of gibberellic acid stereospecifically.<sup>30</sup> The half acid ester 145 (scheme XV), which was derived from gibberellic acid (3a), gave the hydroxy lactone 146 when reacted with *m*-chloro perbenzoic acid. Hydrolysis of 146 followed by iodolactonization gave the iodolactone 147. After trifluoroacetylation and reduction with Zn in AcOH, the iodolactone 147 was converted to methyl gibberellate (3b). In a later study<sup>31</sup> Corey and Danheiser were able to synthesize a model compound 153 which is similar to the gibberellin degradative product 145 by utilizing as the key step an intramolecular Diels-Alder reaction on the ester 150. The ester 150 was derived from condensing the unsaturated alcohol 149 with propiolic acid. The product from the Diels-Alder reaction, lactone 151, was methylated to give the lactone

## Scheme XIV

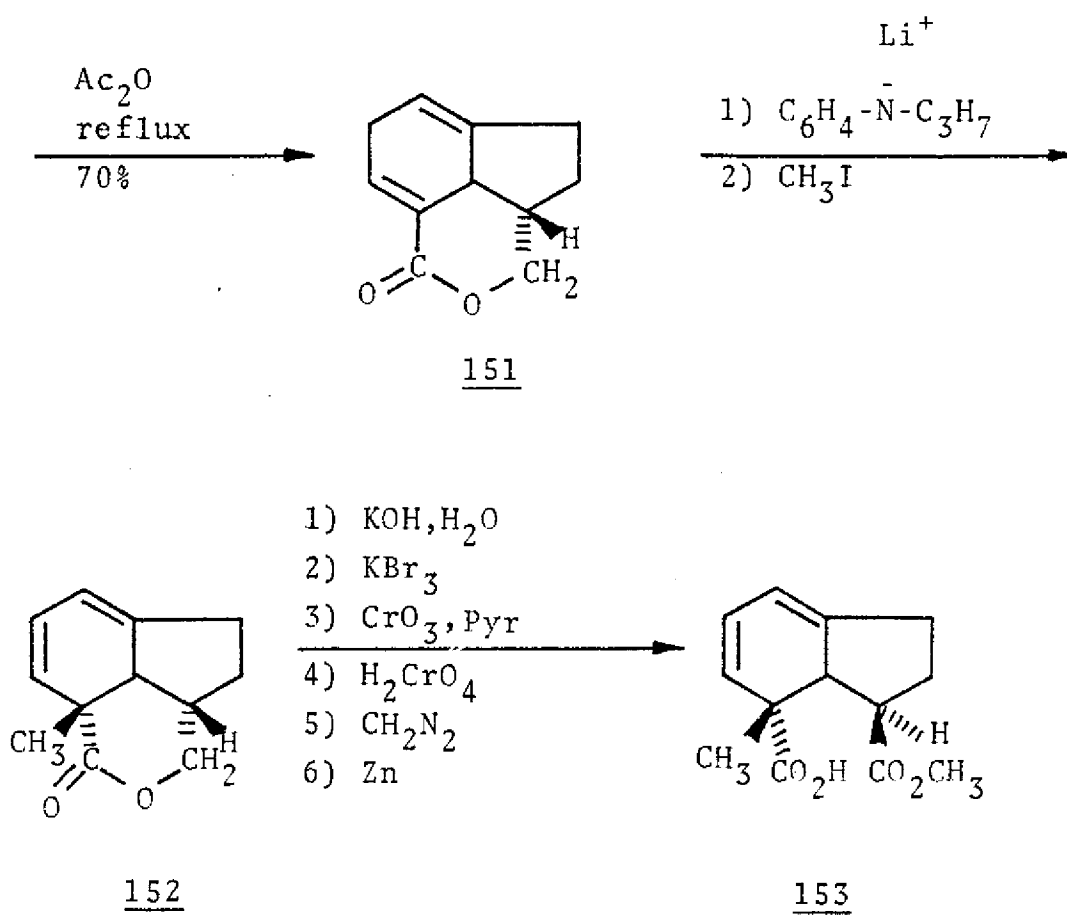




Scheme XV



## Scheme XV (cont.)



152. This compound was converted to the acid ester 153 by the sequence of reactions shown in scheme XV. It was necessary to protect the carboxyl group of the initial hydrolysis product as a bromo lactone.

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## CHAPTER II

APPLICATION OF THE REDUCTION-METHYLATION SEQUENCE  
TO 7-METHOXY HEXAHYDROFLUORENE DERIVATIVESDiscussion

The experiments described in this chapter were carried out to study the conversion of the aromatic diacids 1 and 2 (scheme I) to the reduced diacids 3 as a model for the synthesis of the A ring of various gibberellins (e.g. 4) by the method of Lowenthal and coworkers.<sup>1</sup> Using this procedure, the aromatic ring is reduced with a metal in liquid  $\text{NH}_3$  to give an enolate 5 which can then be methylated. It was hoped that the configuration of the carboxyl group at C-9 would allow control over the stereochemistry at C-8 in the product (3).

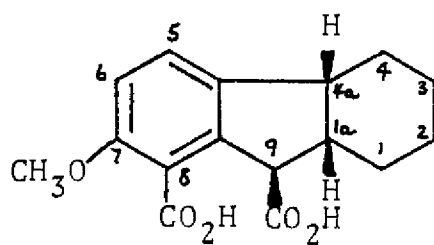
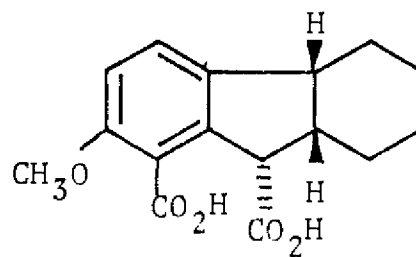
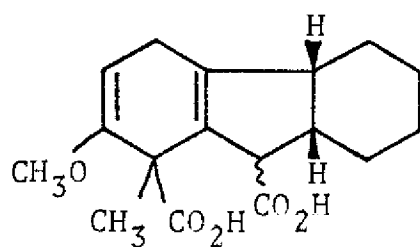
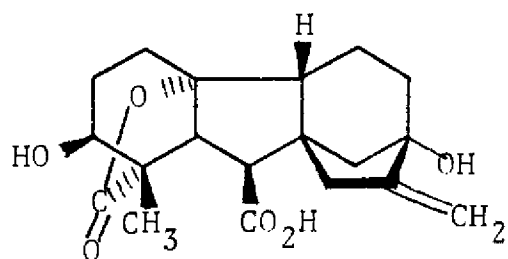
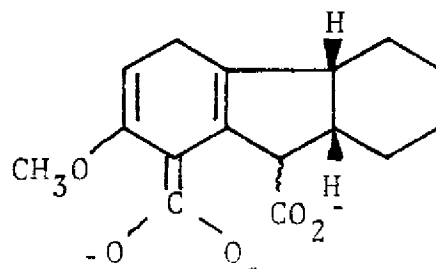
Diacids 1 and 2 were prepared as shown in scheme II according to previously established routes.<sup>2</sup> Some minor modifications are listed below.

1. Rather than  $n\text{-BuLi}$  and  $t\text{-BuONa}$ ,  $n\text{-BuLi}$  alone was found to be adequate for the regiospecific metalation of alcohol 13.

2. A selective esterification of diacids 17 and 18 with  $\text{CH}_3\text{OH}$  and  $\text{BF}_3\text{-Et}_2\text{O}$  was used to facilitate the purification of diester 19.

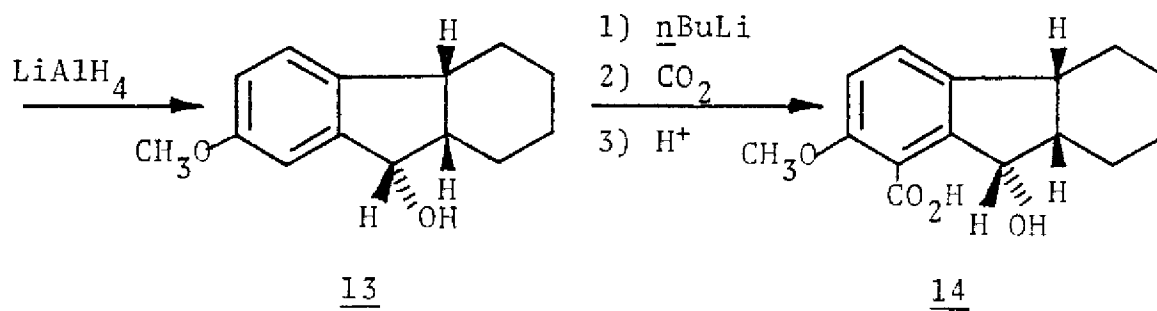
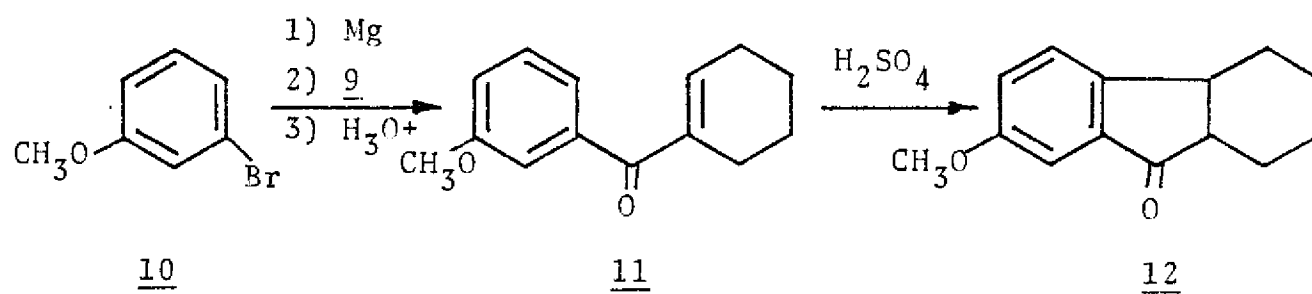
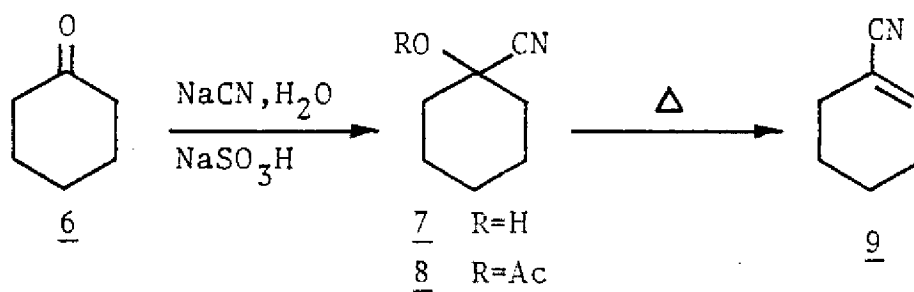
3. Rather than  $\text{CH}_3\text{Li}$  in  $\text{Et}_2\text{O-THF}$ ,  $n\text{-BuLi}$  in hexane

Scheme I

12345



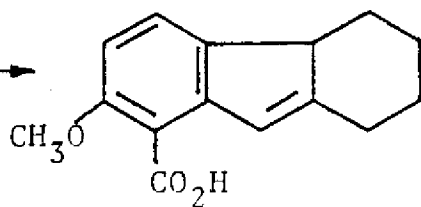
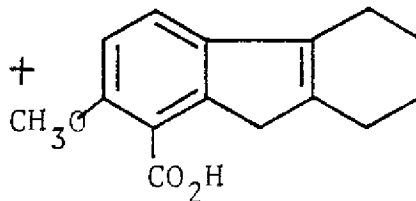
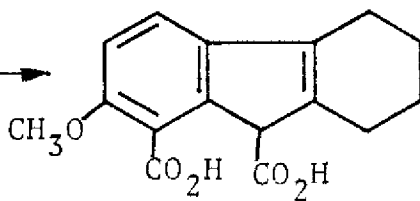
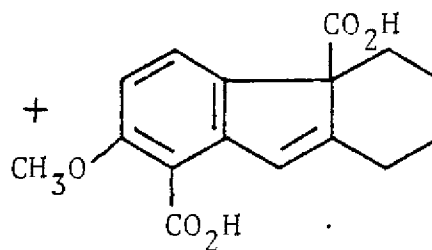
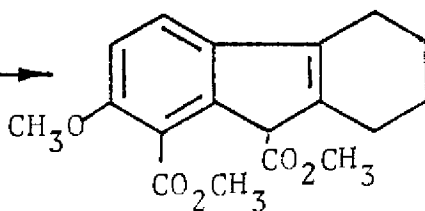
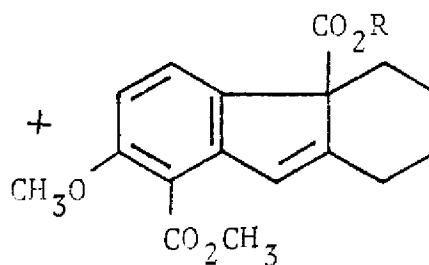
Scheme II



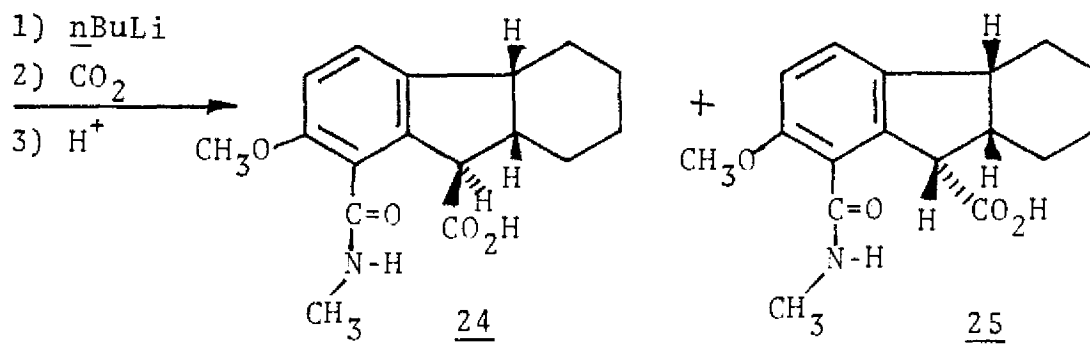
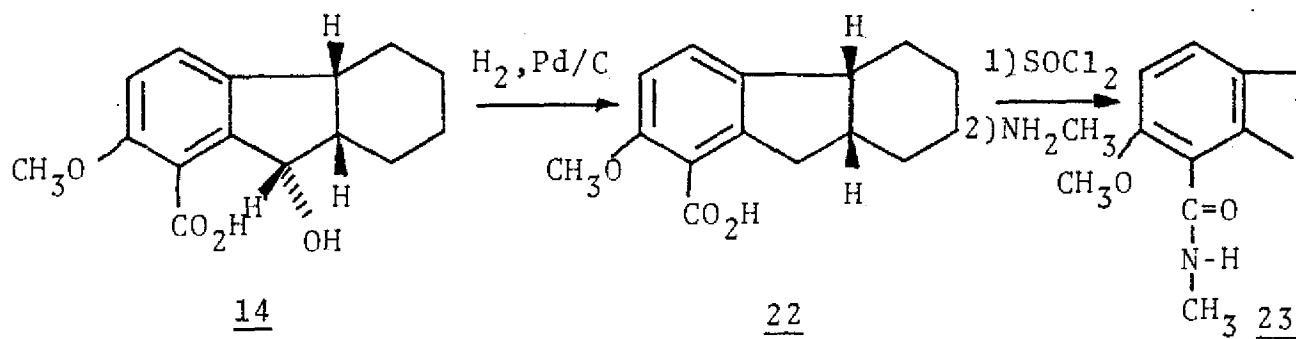
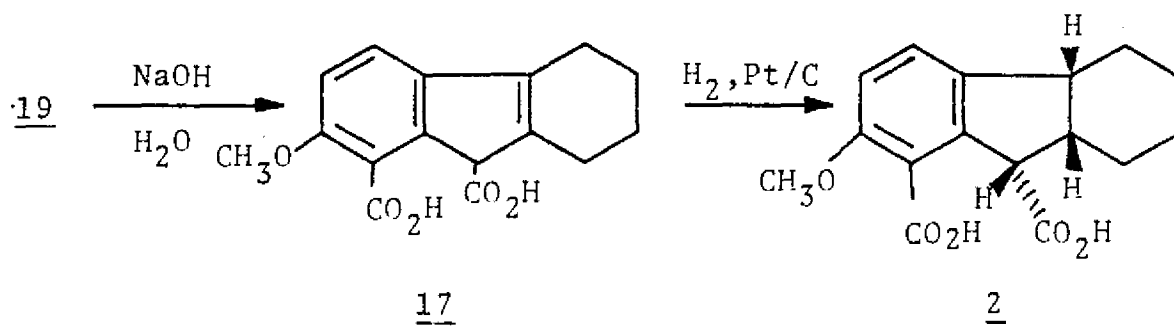
## Scheme II (cont.)

PTSA

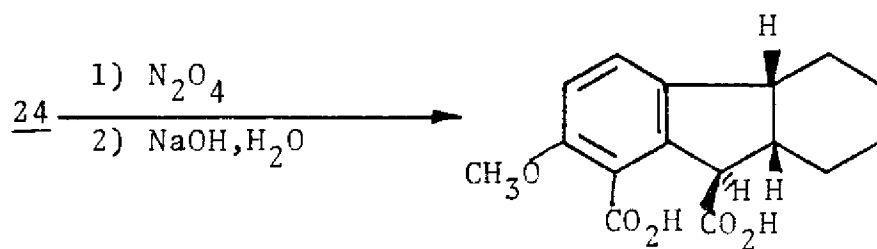
PhH

15161)  $n\text{BuLi}$ 2)  $\text{CO}_2$ 3)  $\text{H}^+$ 1718 $\text{CH}_3\text{OH}$  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ 1920 R=H21 R=CH<sub>3</sub>

## Scheme II (cont.)



## Scheme II (cont.)

1

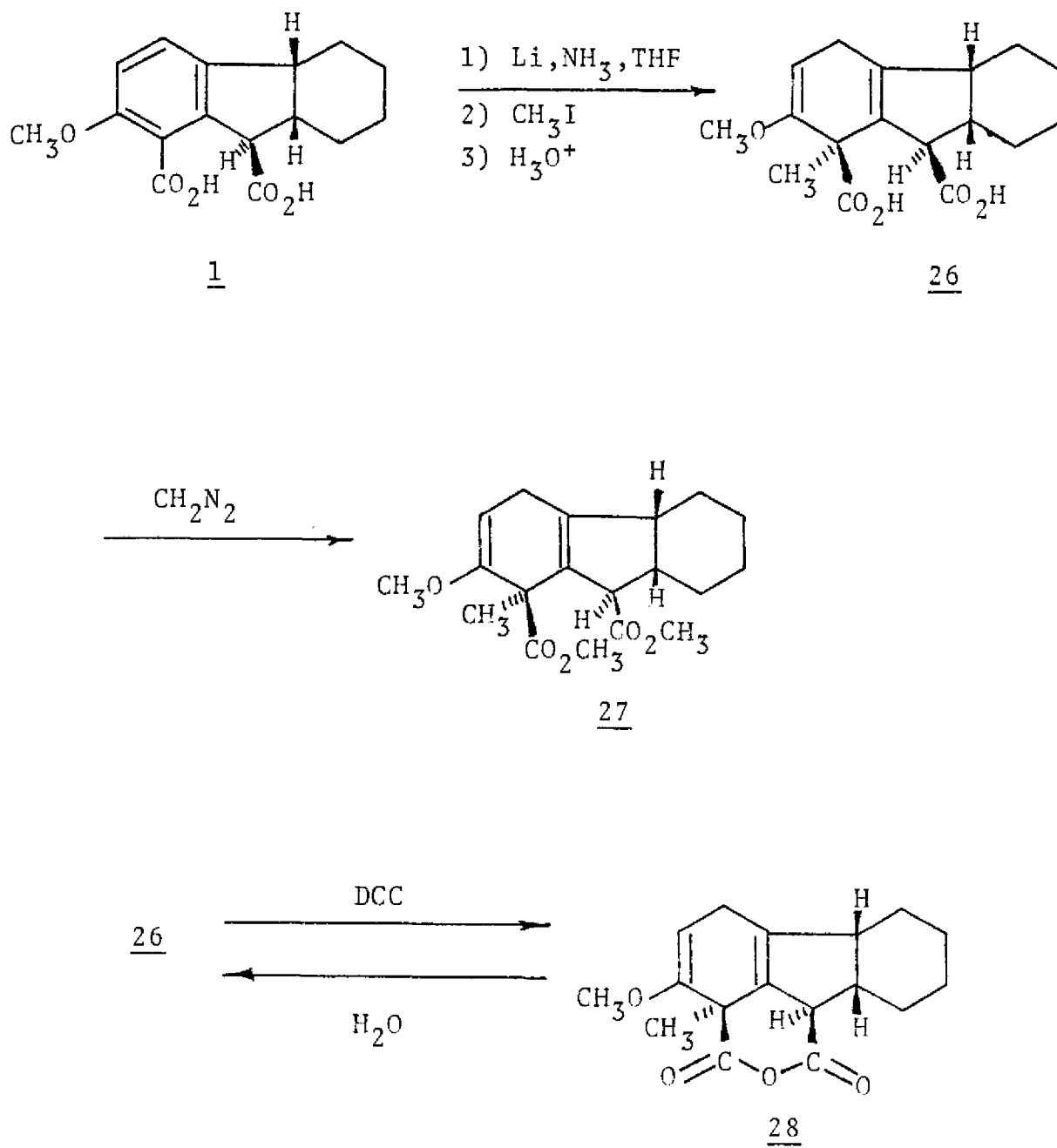
was used to metalate the unsaturated acids 15 and 16.

4. The amido acid 24 was hydrolyzed directly to the diacid 1 by means of an intermediate nitrosoamide<sup>3</sup> rather than by first converting it to the methyl ester and thermally decomposing the nitroso derivative of this compound to the diester of 1.

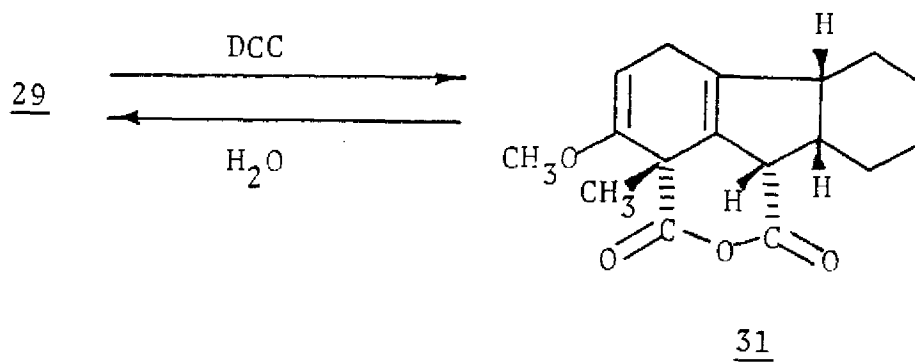
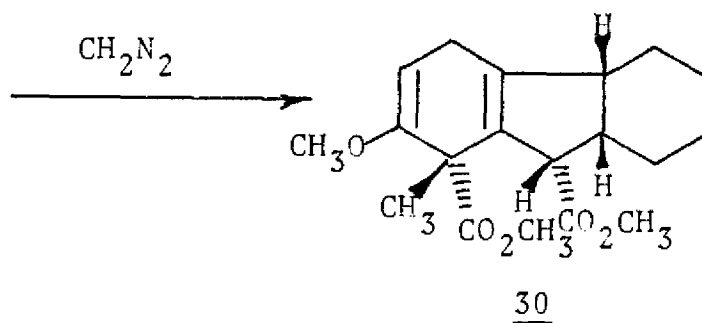
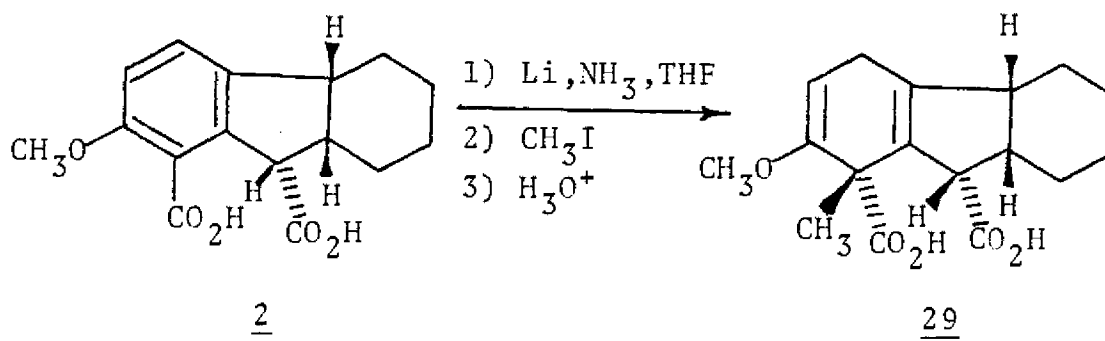
The diacid 1 (scheme III) was reduced with a large excess (45-50 equivalents) of lithium metal in liquid ammonia-THF and alkylated with  $\text{CH}_3\text{I}$  to give the ether insoluble diacid 26 in 50% yield as well as an ether soluble byproduct. If only a stoichiometric amount (4 equivalents) of metal was used, the major product appeared to be derived from protonation of the intermediate enolate anion before the addition of  $\text{CH}_3\text{I}$ . Since the coupling constant ( $J=4$  hz) between the hydrogens at C-1a and C-9 in the corresponding diester 27 was identical to this value for diacid 1, the center at C-9 had not epimerized. Treatment of the diacid 26 with dicyclohexylcarbodiimide in  $\text{CH}_2\text{Cl}_2$  gave the anhydride 28, which could be hydrolyzed back to the diacid 26 to show that epimerization had not taken place at C-9 during the formation of the anhydride.

In the same manner, diacid 2 was reduced and alkylated to give a different ether insoluble diacid 29 in 42% yield and an ether soluble byproduct. The coupling constant ( $J=7$  hz) between the hydrogens at C-1a and C-9 for diacid 29 was also identical to the value for the aromatic diacid 2,

## Scheme III



## Scheme III (cont.)



again showing that epimerization had not occurred at C-9. Reaction of diacid 29 with dicyclohexylcarbodiimide in  $\text{CH}_2\text{Cl}_2$  gave an anhydride 31 which could be hydrolyzed back to diacid 29 to show that epimerization had not occurred during the formation of the anhydride.

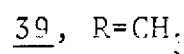
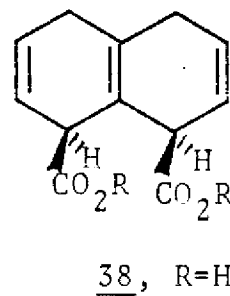
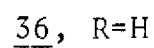
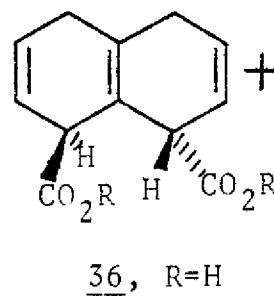
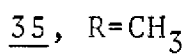
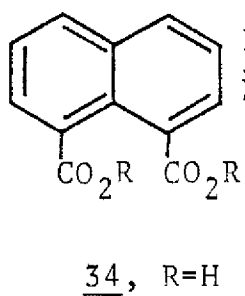
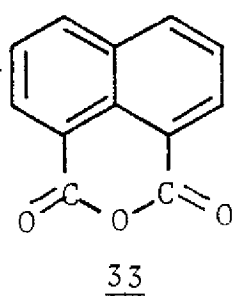
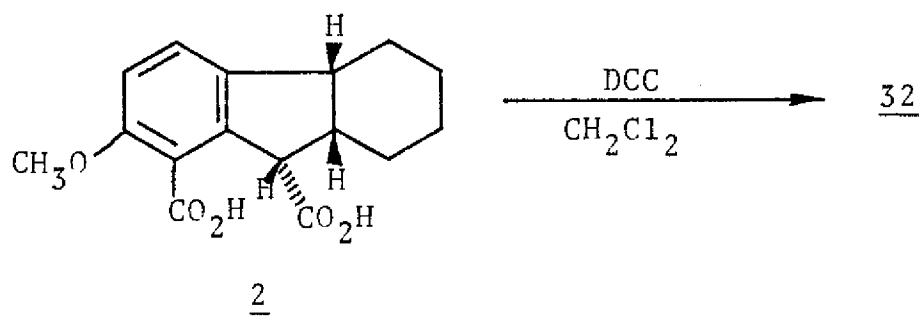
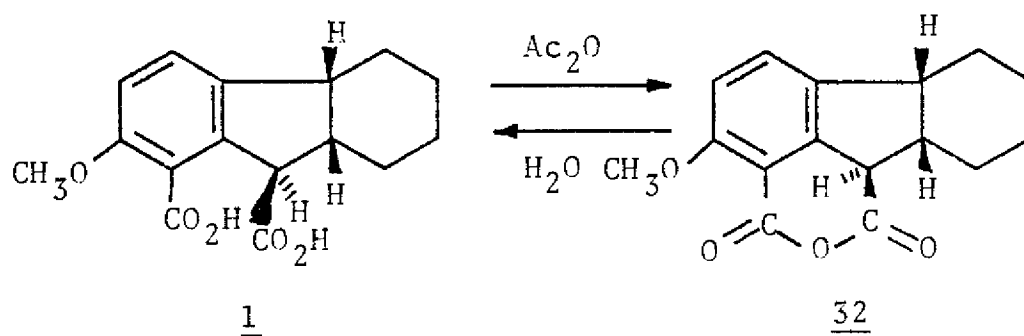
The two bands in the carbonyl region of the infrared spectra of the anhydrides 28 and 31 had absorbance ratios (the ratio of the absorbance of the lower frequency band to that of the higher frequency band) in the range 1.4-1.6. These values are typically 2-3 for unstrained six membered cyclic anhydrides, 7-11 for five membered cyclic anhydrides, and approximately 1 for acyclic anhydrides.<sup>4</sup> Since both anhydrides 28 and 31 had the infrared spectra expected of unstrained six membered cyclic anhydrides, and since both anhydrides could be hydrolyzed to the starting diacids, it follows that the relative configuration of the two carboxyl groups is syn for both diacid 26 and 29. Also, since it was apparent that epimerization at C-9 had not occurred during the reduction, methylation sequence, methylation of the enolate 5 must have taken place from the side opposite to that which contained the C-9 carboxyl group.

The results of the following experiments provided further evidence for these stereochemical assignments;

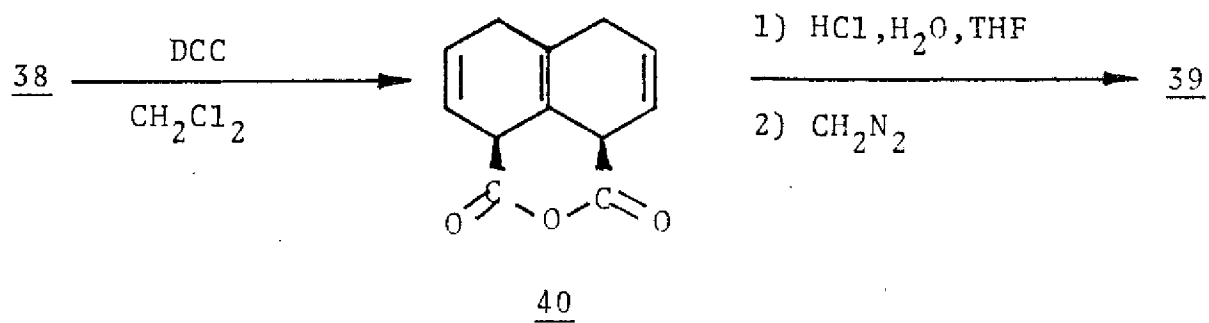
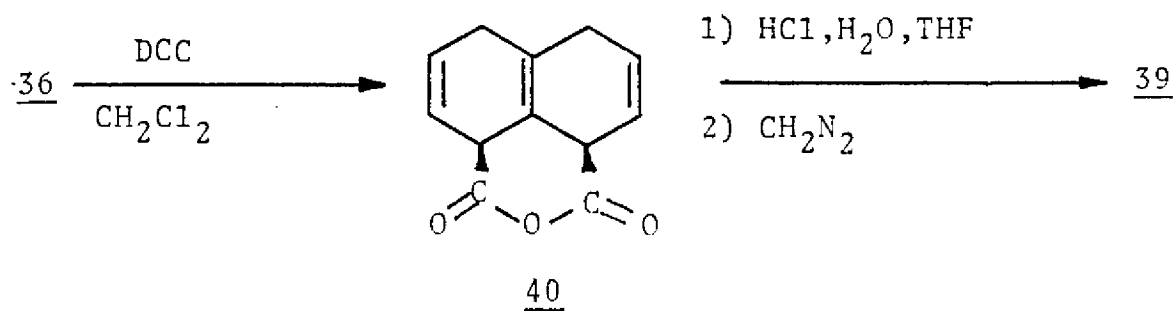
1. When diacid 1 (scheme IV) was refluxed with acetic anhydride, the anhydride 32 was isolated. Anhydride 32



Scheme IV



## Scheme IV (cont.)

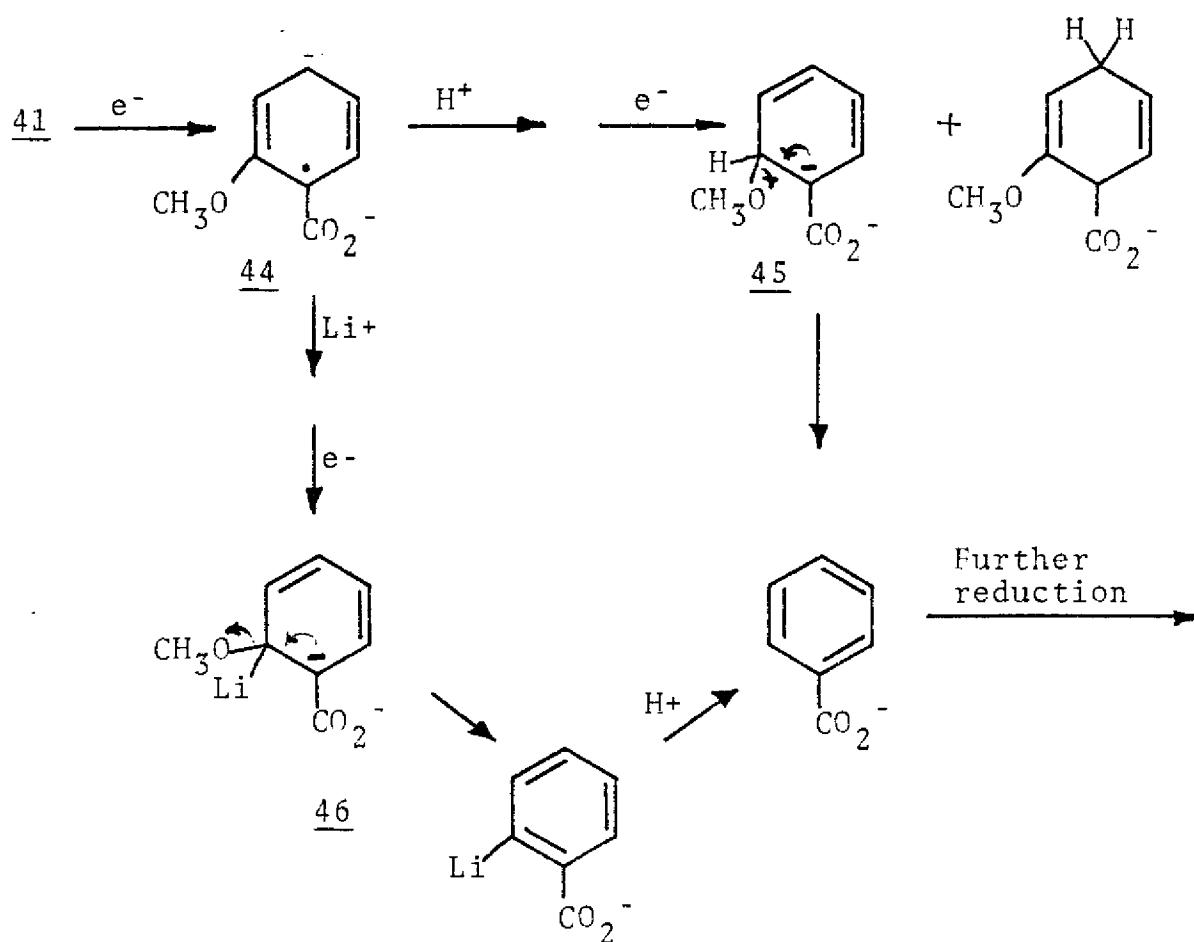
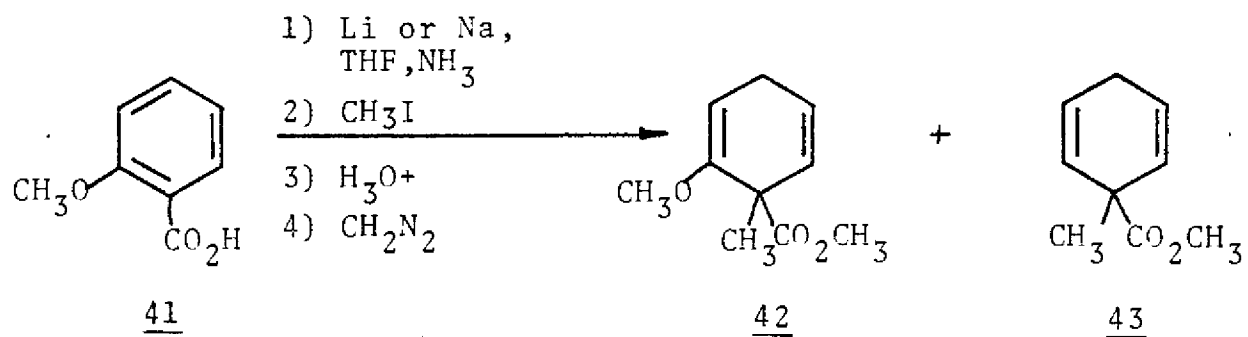


could be hydrolyzed back to diacid 1. When diacid 2 with the less stable configuration at C-9<sup>2a</sup> was stirred with dicyclohexylcarbodiimide at 25°, the center at C-9 was epimerized, and the same anhydride 32 was recovered.

2. The diacid 34 was reduced with Li in NH<sub>3</sub> to give mainly the diacid 36, which could be purified by recrystallization. Equilibration of a mixture of diacids 36 and 38 with base gave mainly diacid 38, which could also be purified by fractional recrystallization. Each of the diacids 36 and 38 was stirred with dicyclohexylcarbodiimide in CH<sub>2</sub>Cl<sub>2</sub> at 25°, and the crude anhydride that formed from each diacid was hydrolyzed and esterified to give the same diester 39. The anhydride intermediate was too unstable to be obtained pure, but spectral data indicated that it was the same compound in both cases; and the infrared spectrum was that expected of an unstrained six membered cyclic anhydride (absorbance ratio, A 1762/1804 = 1.69). It was concluded that the anti diacid 36 was epimerized during the formation of the anhydride, while the syn diacid 38 remained unchanged.

To gain some insight into the nature of the byproducts formed during the reduction, methylation sequence, the methoxy acid 41 (scheme V) was reduced and methylated under similar conditions; and the crude product was esterified with CH<sub>2</sub>N<sub>2</sub>. Along with the expected ester 42, the ester 43 which lacks the methoxy group was also isolated. Less of this byproduct was formed when the reduction was carried out using Na

Scheme V



instead of Li metal. A reasonable mechanism for the loss of the methoxy group is shown in scheme V. Protonation of the initially formed radical anion 44-adjacent to the methoxy group and subsequent elimination rearomatizes the ring. Alternatively, the C-Li bond in 46 could be sufficiently strong to allow elimination of the methoxy group to give 47. The difference in the product mixture when Na and Li are used as the reducing agents may reflect the difference in strengths of the C-metal bonds.

The results of the above experiments showed that intermediates similar to diacids 1 and 2 may be useful in the synthesis of gibberellins, and that the C-9 carboxyl group can be used to control the stereochemistry of the product from the reduction, methylation sequence.

### Experimental Section<sup>5</sup>

#### Preparation of Cyanocyclohexene (9)

Following a procedure described previously,<sup>6</sup> a solution of 588 g (5.66 mol) of sodium bisulfite dissolved in 1125 ml of water was added with stirring and cooling to a mixture of 295 g (6.00 mol) of sodium cyanide, 750 ml of water, and 294 (3.00 mol) of cyclohexanone. After stirring for 3 hr at 25°, the previously described isolation procedure gave 404 g (108%) of crude cyanohydrin 7;  $\text{ir}(\text{CCl}_4)$ ,  $3440 \text{ cm}^{-1}(\text{OH})$ ,  $2240 \text{ cm}^{-1}(\text{C}\equiv\text{N})$ . Using a modification of an earlier procedure,<sup>7</sup> 316 g (2.53 mol) of the crude cyanohydrin

was added to 275 g of refluxing acetic anhydride that contained 3.3 g (0.045 mol) of acetyl chloride over a period of 45 min. The reaction mixture was allowed to reflux for an additional 1.5 hr and then added dropwise to a glass tube packed with glass beads and heated to 575°. The products were swept from the hot tube into a cold trap with a stream of nitrogen. Most of the acetic acid was removed from the pyrolysis product by distillation at 1 atm, and the remaining liquid was dissolved in 500 ml of Et<sub>2</sub>O. The Et<sub>2</sub>O solution was washed with saturated aqueous NaHCO<sub>3</sub> and with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, and concentrated. The residue was distilled through a 20 cm Vigreux column. After a forerun (bp 64-81° at 14 mm) containing by glc analysis (silicone SE-30 on chromosorb P) a mixture of cyclohexanone (retention time 2.0 min) and unsaturated nitrile 9 (retention time 3.0 min), 86.3 g of the pure unsaturated nitrile 9 was collected: bp 81-85° (14 mm);  $\underline{n}^{25}_D$  1.4810 [lit.<sup>6</sup> bp 86° (18 mm);  $\underline{n}^{20}_D$  1.4818]. The forerun was washed with aqueous sodium bisulfite and redistilled to give an additional 53.3 g of unsaturated nitrile 9; bp 80-85° (15 mm);  $\underline{n}^{25}_D$  1.4799. This last fraction contained about 5% cyclohexanone by glc analysis. The total yield of unsaturated nitrile 9 was 139.6 g (54% based on cyclohexanone).

#### Preparation of Unsaturated Ketone 11

Following a procedure described previously,<sup>2a</sup> a mixture of 100g (0.534 mol) of m-bromoanisole (10), 14.3g

(0.588 mol) of magnesium metal, and 640 ml of anhydrous ether (commercial) was heated to maintain a gentle reflux for 1.5 hr. To the resulting brown suspension of the Grignard reagent was added 53.6g (0.500 mol) of the unsaturated nitrile 9 dissolved in 640 ml of anhydrous ether. The reaction mixture was heated to maintain a gentle reflux for 1.0 hr. The reaction mixture, which consisted of a yellow solution and a brown viscous precipitate, was then poured into 1200 ml of aqueous 4 M HCl, and the layers were separated. The ether layer was washed with aqueous 4 M HCl, dried over  $\text{MgSO}_4$ , and concentrated. The residue was 21.6g of brown liquid which consisted of mainly anisole and nitrile 9 by nmr analysis. The aqueous layer was heated on a steam bath for 18 hr, during which time a brown viscous liquid separated. The two phase system was extracted with ether, and the ether extract was washed with saturated aqueous  $\text{NaHCO}_3$  and saturated NaCl. After the  $\text{Et}_2\text{O}$  solution had been dried over  $\text{MgSO}_4$  and concentrated, 76.3g of brown liquid remained. Fractional distillation separated a forerun of 1.04g and 66.2g (61%) of the unsaturated ketone 11: bp 124-129° (0.2 mm);  $n_D^{25}$  1.5652 (lit bp 129-134° at 0.5 mm, <sup>2a</sup> 164-167° at 4 mm<sup>8</sup>).

#### Preparation of the Ketone 12

Following a procedure described previously,<sup>2a</sup> 57.3g (0.266 mol) of the unsaturated ketone 11 was added with stirring to 500 ml of concentrated sulfuric acid at 25° over a period of 30 min. The resulting dark red solution was

stirred for an additional 10 min and then poured into 2000 ml of water and ice. The aqueous suspension was extracted with ether, and the ether extract was washed successively with saturated aqueous  $\text{NaHCO}_3$  and with saturated aqueous  $\text{NaCl}$ , dried over  $\text{MgSO}_4$ , and concentrated. Recrystallization of the crude product (57g) from hexane gave 36.2g of the ketone 12, mp  $97.5-99^\circ$ , and an additional 8.6g of less pure material, mp  $96-99^\circ$  (lit.<sup>2a,8</sup> mp  $99-100^\circ$ ). The total yield of ketone 12 was 44.8g (79%).

#### Preparation of the Alcohol 13

Following a procedure described previously,<sup>2a</sup> a solution of 50.2g (0.232 mol) of the ketone 12 in 300 ml of anhydrous THF was added to a cold ( $0^\circ$ ) suspension of 3.7g (97.5 mol) of  $\text{LiAlH}_4$  in 100 ml of THF. The previously described isolation procedure gave 44.5g (88%) of the alcohol 13 as colorless needles from hexane- $\text{CH}_2\text{Cl}_2$ , mp  $144-145^\circ$  (lit.<sup>2a</sup> mp  $147-147.5^\circ$ ).

#### Preparation of the Hydroxy Acid 14

Following a procedure described previously,<sup>2a</sup> to a cold ( $0^\circ$ ) suspension of 44.4 g (0.204 mol) of the alcohol 13 in 250 ml of hexane was added, dropwise and with stirring during 30 min, 320 ml of a hexane solution containing 0.525 mol of  $n\text{-BuLi}$ . The resulting orange solution was stirred at  $25^\circ$  for 28 hr. Then the resulting suspension was cooled to  $-78^\circ$  and  $\text{CO}_2$  was passed through the solution with vigorous stirring for 45 min. The reaction mixture was treated with



$\text{CH}_2\text{Cl}_2$  and aqueous  $\text{Na}_2\text{CO}_3$  and the precipitate, the Na salt of the acid 14 was collected by filtration. This Na salt was stirred with aqueous HCl and then the mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . After the  $\text{CH}_2\text{Cl}_2$  extract had been dried, concentration left 43.9 g (82%) of the hydroxy acid 14 as a white solid, mp 133-135° (lit. mp 136-137°, <sup>2a</sup> 134-135°<sup>2b</sup>), identified with previously described samples by comparison of ir spectra.

#### Preparation of the Unsaturated Acid 15

Following a procedure described previously,<sup>2a</sup> a solution of 20.0 g (76 mmol) of the acid 14 and 1.9 g (10 mmol) of TsOH in 450 ml of benzene was refluxed with continuous separation of  $\text{H}_2\text{O}$  for 1 hr. It was then washed with  $\text{H}_2\text{O}$ , dried, and concentrated to leave 17.5 g of the crude acid 15 as a yellow solid, mp 145-154°. Fractional recrystallization ( $\text{CH}_2\text{Cl}_2$ -hexane) separated 12.7 g of early fractions of white prisms, mp 151-157° (lit.<sup>2a</sup> mp 161.5-162.5°), containing (ir analysis) mainly the acid 15. Later fractions (4.1 g, mp 125-145°) contained (nmr analysis) the acid 15 accompanied by increasing amounts of the isomeric acid 16. The total yield of the mixture of isomeric acids 15 and 16 (suitable for further reaction with  $n\text{-BuLi}$ ) was 16.8 g (90%).

#### Preparation of the Diacid 17

To a cold (0°) suspension of 16.5 g (67.6 mmol) of the unsaturated acid 15 (containing some of the isomeric acid 16) in 180 ml of  $\text{Et}_2\text{O}$  and 180 ml of THF was added, dropwise

and with stirring, 100 ml of a hexane solution containing 156 mmol of n-BuLi. The resulting red solution was stirred at 25° for 1 hr and then siphoned onto crushed dry ice. The reaction mixture was partitioned between Et<sub>2</sub>O and aqueous Na<sub>2</sub>CO<sub>3</sub> and the aqueous phase was acidified. The precipitate of crude diacids 17 and 18 was collected, combined with the CH<sub>2</sub>Cl<sub>2</sub> extract of the aqueous filtrate, and the CH<sub>2</sub>Cl<sub>2</sub> suspension was concentrated without drying. The residual solid was dried under reduced pressure over P<sub>2</sub>O<sub>5</sub> and then washed several times with ether to leave 13.9 g of a light brown solid containing (nmr analysis, CH<sub>3</sub>O peaks at δ 3.75 and 3.80) an approximately equal mixture of the diacids 17 and 18. A solution of this mixture of diacids and 5.0 ml of BF<sub>3</sub>·Et<sub>2</sub>O in 400 ml of MeOH<sup>9</sup> was refluxed for 23 hr and then concentrated and partitioned between aqueous Na<sub>2</sub>CO<sub>3</sub> and CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried and concentrated to leave 9.7 g of orange liquid containing [liquid chromatography, C-18 Corasil column with a H<sub>2</sub>O-CH<sub>3</sub>CN (3:2 v/v) eluent] the diester 19 (ca. 70%, ret. time 2.0 min), the diester 21 (ca. 30%, 1.5 min), and two minor unidentified impurities (4.1 and 8.2 min). Fractional crystallization from Et<sub>2</sub>O separated 4.53 g of the crude diester 19, mp 86-86.5°, that was recrystallized from MeOH to give 3.98 g of diester 19 as white needles, mp 88-89° (lit.<sup>2a</sup> 91-91.5°). The remaining materials from the mother liquors were chromatographed on silica gel (eluent PhH-Et<sub>2</sub>O, 99:1 v/v) and

subsequently crystallized to separate an additional 1.08 g (total yield 5.06 g or 26%) of the diester 19, mp 88-89.5°. A mixture of 3.98 g (12.6 mmol) of the diester 19, 1.90 g (47.4 mmol) of NaOH, and 75 ml of H<sub>2</sub>O was refluxed for 45 min and the resulting orange solution was acidified. The crude product, collected on a filter, was recrystallized from aqueous MeOH to separate 3.117 g (86%) of the diacid 17 as a pale yellow solid, mp 197° dec (lit.<sup>2a</sup> mp 200 dec), that was identified with a previously described sample by comparison of ir spectra.

#### Preparation of the Diacid 2

Following a procedure described previously,<sup>2a</sup> a solution of 3.102 g (10.8 mmol) of the diacid 17 in 50 ml of THF and 50 ml of HOAc was hydrogenated at 1 atm and 27° over 573 mg of 5% Pt-on-C catalyst until the hydrogen uptake (9.74 mmol or 0.90 equiv) ceased. The mixture was filtered and concentrated to leave 3.053 g of crude product, mp 185-203° dec, that was recrystallized from an acetone-hexane mixture. The yield of the diacid 2 was 2.647 g (85%) of white needles, mp 198-206° dec (lit.<sup>2a</sup> mp 201-203° dec) identified with a previously described<sup>2a</sup> sample by comparison of nmr spectra.

#### Preparation of the Acid 22

Following a procedure described previously,<sup>2b</sup> 39.0 g (0.149 mol) of the alcohol 14 was dissolved in 250 ml of THF containing 50 ml of acetic acid and 0.2 ml of 70% HClO<sub>4</sub>,

and hydrogenated at 40 psi over 2.0 g of 5% Pd/c in a Parr hydrogenation apparatus. The uptake of hydrogen was complete after 30 min, and the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in Et<sub>2</sub>O, washed with H<sub>2</sub>O, and dried over MgSO<sub>4</sub>. Concentration of the Et<sub>2</sub>O solution left a yellow liquid which partially crystallized on standing under hexane. The crystals were collected and washed with hexane, giving 24.5 g of the acid 22 as colorless plates, mp 91.5-94° (lit.<sup>2b</sup> mp 93-94°). The solvent was removed from the filtrate, leaving a liquid which slowly solidified when allowed to stand under reduced pressure. This material was recrystallized from hexane-CH<sub>2</sub>Cl<sub>2</sub> to give 7.2 g of colorless plates, mp 91-93°. The total yield of acid 22 was 31.7 g (87%).

#### Preparation of the Amide 23

Following a procedure described previously,<sup>2b</sup> 31.7 g (0.130 mol) of the acid 22 was stirred at 25° with 150 ml of SOCl<sub>2</sub> for 17 hr. After excess SOCl<sub>2</sub> had been removed under reduced pressure, a solution of the residual acid chloride in 250 ml of THF was added with vigorous stirring to 400 ml of 40% methylamine in water. The resulting white precipitate was collected by filtration. The filtrate was diluted with water, cooled in an ice bath, and filtered again. The collected solid was combined and dissolved in CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> solution was washed successively with saturated aqueous NaHCO<sub>3</sub> and with saturated aqueous NaCl, dried over

MgSO<sub>4</sub>, and concentrated to leave 32.0 g of crude amide, mp 160-162°. After two recrystallizations from methanol, 27.5 g (82%) of the pure amide 23 separated as colorless needles, mp 167-168° (lit.<sup>2b</sup> mp 168-169°).

Preparation of Diacid 1 from the Amide 23

Following a previous procedure,<sup>2b</sup> a cold (0°) suspension of 2.692 g (10.4 mmol) of the amide 23 in 30 ml of THF was treated with 20 ml of a hexane solution containing 31.2 mmol of *n*-BuLi and the resulting mixture was stirred at 0° for 1 hr and at reflux for 30 min. After the resulting orange suspension had been diluted with 30 ml of THF, it was poured onto crushed dry ice. The crude acidic product, isolated in the usual way, amounted to 1.659 g of an Et<sub>2</sub>O-soluble fraction and 1.020 g of a less soluble fraction containing (tlc, silica gel with a CHCl<sub>3</sub>-EtOAc-HCO<sub>2</sub>H eluent, 10:10:3 v/v/v) the amide acids 24 (R<sub>f</sub> 0.51) and 25 (R<sub>f</sub> 0.41). Repeated extraction with Et<sub>2</sub>O left 497 mg of the less soluble amide acid 25, mp 212-214 dec, that was triturated with acetone to leave 434 mg (14%) of the pure (tlc) amide acid 25, mp 212 dec (lit.<sup>2b</sup> mp 213-215°). This material was identified with a previously described sample by comparison of ir spectra. The combined Et<sub>2</sub>O-soluble portions of the crude acidic product were concentrated to leave 2.179 g (70%) of the crude acid amide 24 (tlc analysis). Recrystallization from EtOH afforded 1.70 g (55%) of the pure acid amide 24 as white needles, mp 150-152° (lit.<sup>2b</sup> 152-153°), identified with

a previously described sample by comparison of ir spectra. In the present studies, the mixture of amide acids 24 and 25 obtained from this metalation-carbonation procedure has consistently contained a greater amount of the amide acid 24 whereas the stereoisomer 25 was the predominant product in earlier work.<sup>2b</sup> The reason for this difference is not apparent.

A cold (ca. 15°) solution of 515 mg (1.70 mmol) of the amide acid 24 and 220 mg (2.68 mmol) of NaOAc in 15 ml of HOAc was treated with 0.5 ml (ca. 7 mmol) of N<sub>2</sub>O<sub>4</sub> and the resulting green solution was stirred for 15 min during which time a yellow solid separated. After the mixture had been partitioned between H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub>, the CH<sub>2</sub>Cl<sub>2</sub> layer was dried and concentrated to leave 617 mg of the crude nitroso compound as an orange liquid containing (tlc, silica gel with a CHCl<sub>3</sub>-EtOAc-HCO<sub>2</sub>H eluent, 10:10:3 v/v/v) one major component (R<sub>f</sub> 0.68) and lacking the starting amide 24 (R<sub>f</sub> 0.43). The crude product was added to 25 ml of cold (0°) aqueous 10% NaOH and then stirred at 0° for 15 min and at reflux for 15 min. Gas evolution was apparent as the solution was warmed above 0°. The resulting dark brown solution was acidified (HCl) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. After the CH<sub>2</sub>Cl<sub>2</sub> solution had been dried and concentrated, trituration with ether left 364 mg of the crude diacid 1 as a brown solid, mp 184-185°. After an acetone solution of the product had been decolorized with carbon, crystallization from acetone-hexane mixtures separated 222 mg (45%) of the diacid 1 as a

tan solid, mp 188-190° (lit.<sup>2a</sup> 189.5-190.5°), that was identified with a previously described sample by comparison of nmr spectra.

#### Reductive Methylation of the Diacid 1

To a refluxing (-33°) solution of 758 mg (108 mg atom) of Li in 100 ml of liquid NH<sub>3</sub> was added, dropwise and with stirring during 20 min, a solution of 659 mg (2.27 mmol) of the diacid 1 in 20 ml of THF.<sup>10</sup> After the addition was complete, the resulting blue reaction mixture was stirred for 5 min and then 8.0 ml (18.4 g or 128 mmol) of CH<sub>3</sub>I was added. As the CH<sub>3</sub>I was added the blue reaction mixture changed progressively to a white suspension, a colorless solution, and finally a green solution. After the addition was complete, the reaction mixture was stirred for 30 min and then 5 ml of CH<sub>3</sub>OH was added followed by 5 ml of H<sub>2</sub>O and the NH<sub>3</sub> was allowed to evaporate. The remaining mixture was concentrated under reduced pressure, diluted with 50 ml of cold water, acidified to pH 4 with aqueous 1 M HCl, and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> extract was dried and concentrated to leave 733 mg of crude yellow semisolid. Trituration of this residue with Et<sub>2</sub>O left 351 mg (50.5%) of the crude diacid 26 as a white solid, mp 175-176° dec. The Et<sub>2</sub>O-soluble material from this separation contained (nmr analysis) little, if any, of either methylated diacid 26 or 29. Recrystallization from MeOH separated the diacid 26<sup>11</sup> as white prisms, mp 180-181.5° dec; ir (KBr pellet), 2920

(broad, assoc, OH), 1710 (broad, carboxyl C=O), and  $1660\text{ cm}^{-1}$  (C=C); uv (95% EtOH), end absorption with  $\epsilon$  3900 at 210 m $\mu$ ; nmr (pyridine),  $\delta$  4.90 (1H, t,  $J = 3.5\text{ Hz}$ , vinyl CH), 3.3-3.8 (4H, m, CH-CO<sub>2</sub>R and CH<sub>3</sub>O singlet at 3.56), and 1.0-3.3 (15H, m, aliphatic CH including a CH<sub>3</sub> singlet at 1.90); mass spectrum, m/e (rel. intensity), 262(33), 247(20), 218(100), 203(87), and 91(97). Reaction of 622 mg (2.04 mmol) of the crude diacid 26 with excess ethereal CH<sub>2</sub>N<sub>2</sub> yielded 678 mg (99%) of the crude diester 27. Recrystallization from Et<sub>2</sub>O-hexane afforded 580 mg (85%) of the pure diester 27<sup>11</sup> as white prisms, mp 145.5-147°; ir (CCl<sub>4</sub>), 1740 (ester C=O), 1690 (enol ether C=C), and  $1655\text{ cm}^{-1}$  (C=C); uv (95% EtOH), end absorption with  $\epsilon$  3900 at 210 m $\mu$ ; nmr (CDCl<sub>3</sub>),  $\delta$  4.82 (1H, t,  $J = 3.5\text{ Hz}$ , vinyl CH), 3.63, 3.60, 3.56 (three 3H, s, OCH<sub>3</sub> and CO<sub>2</sub>CH<sub>3</sub>), 3.1-3.3 (1H, m, CHCO<sub>2</sub>R), 2.2-3.0 (4H, m, allylic and aliphatic CH), and 1.0-2.0 (11H, m, aliphatic CH including a CH<sub>3</sub> singlet at 1.47); mass spectrum, m/e (rel. intensity), 334 (M<sup>+</sup>, 0.5), 275 (11), 274(11), 216(47), 215(100), 173(70), 159(68), 141(62), 129(65), 128(68), 115(68), 91(56), and 59(43). Measurement of the nmr spectrum (CDCl<sub>3</sub>) of the diester 27 with irradiation at  $\delta$  2.8 to decouple the allylic CH and CH<sub>2</sub> protons from the C-9 proton left the signal for this C-9 proton as a doublet ( $J = 4\text{ Hz}$ ) at  $\delta$  3.18 corresponding to the coupling constant between protons at C-9 and C-1a.

Anal. Calcd for C<sub>19</sub>H<sub>26</sub>O<sub>5</sub>: C, 68.24; H, 7.84. Found: C, 67.99; H, 7.71.



### Preparation of the Anhydride 28

A solution of 204 mg (0.668 mmol) of the diacid 26 and 162 mg (0.787 mmol) of dicyclohexylcarbodiimide in 7.0 ml of  $\text{CH}_2\text{Cl}_2$  was stirred at  $25^\circ$  for 2 hr during which time a white precipitate of dicyclohexylurea separated. The mixture was filtered and the filtrate was concentrated and triturated with pentane to leave 218 mg of a pale yellow solid. A solution of this material in PhH was centrifuged to remove additional insoluble dicyclohexylurea and then diluted with pentane and cooled to crystallize 143 mg (74.5%) of the anhydride 28 as white needles, mp  $145-147^\circ$  dec. The semi-solid residue (15 mg) recovered from the mother liquors contained (ir analysis) the same anhydride 28. Recrystallization from EtOAc gave the anhydride 28 as white needles mp  $148-150^\circ$  dec (dependent on rate of heating); ir ( $\text{CHCl}_3$ ), 1808 and  $1765\text{ cm}^{-1}$  (anhydride  $\text{C}=\text{O}$ , absorbance ratio  $A_{1765}/A_{1808} = 1.43$ ), nmr ( $\text{CDCl}_3$ ),  $\delta$  4.88 (1H, t,  $J=3.5\text{ Hz}$ , vinyl CH), 3.4 - 3.8 (4H, m,  $\text{CHCO}_2\text{R}$  and a  $\text{CH}_3\text{O}$  singlet at 3.66), 2.3-3.0 (4H, m, CH and allylic  $\text{CH}_2$ ), and 0.8-2.3 (11H, m, aliphatic CH including a  $\text{CH}_3$  singlet at 1.58); mass spectrum, m/e (rel. intensity), 288( $\text{M}^+$ , 1), 260 (38), 217 (31), 216 (100), 215 (31), 201 (48), 185 (38), 174 (50), and 173 (68).

Anal. Calcd for  $\text{C}_{17}\text{H}_{20}\text{O}_4$ : C, 70.81; H, 6.99.

Found: C, 70.83, H, 7.02.

A solution of 62 mg (0.22 mmol) of the anhydride 28

in 2.0 ml of THF and 1 ml of  $H_2O$  was stirred at  $25^\circ$  for 8.5 hr during which time a white solid separated. After the mixture had been concentrated and extracted with  $CH_2Cl_2$ , the  $CH_2Cl_2$  extract was dried and concentrated to leave 66 mg (100%) of the diacid 26, mp  $178^\circ$  dec, that was identified with an authentic sample by comparison of ir and nmr spectra.

#### Reductive Methylation of the Diacid 2

The same procedure used with the diacid 1 was followed with a solution of 862 mg (2.98 mmol) of the diacid 2 in 20 ml of THF being added during 20 min<sup>10</sup> to a solution of 949 mg (135 mg-atom) of Li in 100 ml of liquid  $NH_3$ . After reaction with 10.0 ml (22.8 g or 161 mmol) of  $CH_3I$  and the previously described isolation procedure, the crude acidic product was obtained as 884 mg of yellow semi-solid.

Trituration with  $Et_2O$  left 360 mg (42%) of the diacid 29 as a white solid, mp  $180-190^\circ$  dec. The  $Et_2O$ -soluble material from this separation contained (nmr analyses) little, if any, of either of the methylated diacids 26 or 29. The crude diacid was recrystallized from EtOH to separate the diacid 29<sup>11</sup> as white prisms, mp  $199-201^\circ$  dec; ir (KBr pellet), 2920 (broad, assoc. OH), 1700 (broad, carboxyl C=O), 1660, and 1655 (shoulder)  $cm^{-1}$  (C=C); uv (95% EtOH); end absorption with  $\epsilon$  4200 at 210 m $\mu$ ; nmr (pyridine),  $\delta$  4.86 (1H, t,  $J = 3.5$  Hz, vinyl CH), 3.93 (1H, doublet,  $J = 7$  Hz, of multiplets,  $CH-CO_2R$ ), 3.55 (3H, s,  $OCH_3$ ), 1.82 (3H, s,  $CH_3$ ), and 1.1-3.1 (12H, m, aliphatic CH); mass spectrum, m/e

(rel. intensity), 262 (100), 247 (33), 219 (45), 217 (31), 91 (34), and 44 (55). Because of the thermal instability of the diacid 29 it was converted to the diester 30 for further characterization. Reaction of 270 mg (0.88 mmol) of the diacid 29 with excess ethereal  $\text{CH}_2\text{N}_2$  yielded 284 mg (97%) of the crude diester 30. Recrystallization from ether-hexane afforded 225 mg (77%) of the pure diester 30<sup>11</sup> as white prisms, mp 126-128°; ir ( $\text{CCl}_4$ ), 1738 (ester C=O), 1690 (enol ether C=C), and 1658  $\text{cm}^{-1}$  (C=C); uv (95% EtOH), end absorption with  $\epsilon$  4000 at 210 m $\mu$ ; nmr ( $\text{CDCl}_3$ ),  $\delta$  4.83 (1H, t,  $J$  = 3.5 Hz, vinyl CH), 3.66, 3.63, 3.56, (three 3H, s,  $\text{OCH}_3$  and  $\text{CO}_2\text{CH}_3$ ), 3.4-3.7 (1H, m,  $\text{CHCO}_2\text{R}$ ), 2.3-3.0 (4H, m, allylic and aliphatic CH), and 1.1-1.9 (11H, m, aliphatic CH including a  $\text{CH}_3$  singlet at 1.39); mass spectrum, m/e (rel. intensity), 334 ( $\text{M}^+$ , 1), 275 (15), 274 (15), 216 (31), 215 (100), and 59 (30).

Anal. Calcd for  $\text{C}_{19}\text{H}_{26}\text{O}_5$ : C, 68.24; H, 7.84.

Found: C, 68.19; H, 7.79.

#### Preparation of the Anhydride 31

A mixture of 159 mg (0.52 mmol) of the diacid 29, 129 mg (0.627 mmol) of dicyclohexylcarbodiimide, and 7.0 ml of  $\text{CH}_2\text{Cl}_2$  was stirred at 25° for 2.5 hr. After the resulting suspension had been filtered, the filtrate was concentrated. The residue was triturated with pentane, dissolved in PhH, filtered, and diluted with pentane. The anhydride 31 separated as 96 mg (64%) of white needles, mp 127-130°.

Recrystallization from PhH-pentane gave the pure anhydride 31, mp 128-130°, ir (CHCl<sub>3</sub>), 1805 and 1764 cm<sup>-1</sup> (anhydride C=O, absorbance ratio  $A_{1764}/A_{1805} = 1.55$ ), nmr (CDCl<sub>3</sub>),  $\delta$  4.90 (1H, t, J = 3.5 Hz, vinyl CH), 3.6-4.1 (4H, m, CHCO<sub>2</sub>R and a CH<sub>3</sub>O singlet at 3.67), 2.7-3.1 (4H, m, CH and allylic CH<sub>2</sub>), and 0.8-1.9 (11H, m, aliphatic CH including a CH<sub>3</sub> singlet at 1.50); mass spectrum, m/e (rel. intensity), 288 (M<sup>+</sup>, 2), 260 (70), 242 (45), 217 (51), 216 (100), 215 (38), 201 (41), 199 (39), 185 (42), 174 (48), and 173 (80).

Anal. Calcd for C<sub>17</sub>H<sub>20</sub>O<sub>4</sub>: C, 70.81; H, 6.99.

Found: C, 70.53; H, 7.06.

A solution of 33 mg (0.12 mmol) of the anhydride 31 and 0.2 ml of H<sub>2</sub>O in 1.0 ml of THF was stirred at 25° for 6 hr and then concentrated under reduced pressure. The residual diacid 29 (35 mg or 100% of white solid mp 190° dec) was identified with the previously described sample by comparison of ir and nmr spectra.

#### Preparation of the Anhydride 32

A mixture of 478 mg (1.65 mmol) of the diacid 1 and 6.0 ml of Ac<sub>2</sub>O was refluxed for 1 hr and then concentrated under reduced pressure. The residue was triturated with pentane to leave 393 mg of the crude anhydride 32 as a yellow solid, mp 142-155°. Recrystallization from acetone-hexane separated 205 mg (46%) of the anhydride 32 as white plates, mp 159-161°; ir (CHCl<sub>3</sub>), 1802 and 1760 cm<sup>-1</sup>

(anhydride C=O, absorbance ratio  $A_{1760}/A_{1802} = 1.50$ );  
 nmr ( $\text{CDCl}_3$ ),  $\delta$  7.47 (1H, d,  $J = 8$  Hz, aryl CH), 6.90 (1H, d,  $J = 8$  Hz, aryl CH), 3.8-4.3 [4H, m, benzylic CH doublet ( $J \sim 11$  Hz) at 4.13 partially resolved from a  $\text{CH}_3\text{O}$  singlet at 3.97], and 0.9-3.3 (10H, m, aliphatic CH); uv max ( $\text{Et}_2\text{O}$ ), 321 m $\mu$  ( $\epsilon$  4900) with intense end absorption; mass spectrum, m/e (rel. intensity), 272 ( $\text{M}^+$ , 34), 229 (20), 228 (100), 185 (75), 171 (24), 129 (25), 128 (29), and 115 (29).

Anal. Calcd for  $\text{C}_{16}\text{H}_{16}\text{O}_4$ : C, 70.57; H, 5.92.

Found: C, 70.50; H, 5.92.

After a solution of 36 mg of this anhydride 32 and 1.3 ml of  $\text{H}_2\text{O}$  in 2.0 ml of DME had been heated on a steam bath for 30 min, concentration left 36 mg of the solid acid 1, identified with an authentic sample by comparison of ir spectra.

In an attempt to form the anhydride from the less stable diacid 2, 109 mg (0.376 mmol) of the diacid 2 was added to a solution of 97 mg (0.47 mmol) of dicyclohexylcarbodiimide in 5 ml of  $\text{CH}_2\text{Cl}_2$ . After the resulting suspension had been stirred at  $25^\circ$  for 2.5 hr, it was filtered and the filtrate was concentrated to leave a yellow semisolid. The crude product was washed with pentane, dissolved in PhH and filtered (to remove dicyclohexylurea), and again concentrated to leave 62 mg (60%) of the anhydride 32 as colorless prisms, mp  $156-158^\circ$ . Recrystallization (PhH-pentane) raised

the mp of the anhydride 32 to 159-161°. This product was identified with the previously described sample by a mixed mp determination and by comparison of ir and nmr spectra.

#### Reduction of the Diacid 34

To a cold (-33°) suspension of 10.0 g (47.7 mmol) of the diacid 34 in 600 ml of liquid  $\text{NH}_3$  containing 10 ml of  $\text{H}_2\text{O}$  was added, portionwise and with stirring during 60 min, 2.701 g (386 mg-atom) of Li. An additional 10 ml of  $\text{H}_2\text{O}$  was added and this mixture was stirred overnight while the  $\text{NH}_3$  was allowed to evaporate. A solution of the residue in  $\text{H}_2\text{O}$  was filtered, cooled in ice, and acidified with aqueous 12 M HCl. The resulting cold suspension (total volume 200 ml) was filtered to separate 9.6 g of the crude acids 36 and 38 as a tan solid. To analyze this mixture of acids 36 and 38, an aliquot was esterified with excess ethereal  $\text{CH}_2\text{N}_2$ ; the crude neutral product, a mixture of esters 37 and 39 exhibited nmr peaks ( $\text{CCl}_4$ ) at  $\delta$  3.67 ( $\text{CH}_3\text{O}$  of ester 37) and 3.57 ( $\text{CH}_3\text{O}$  of ester 39).

A commercial sample of the anhydride 33 was recrystallized from concentrated aqueous  $\text{HNO}_3$  to separate the pure anhydride 33 as white needles, mp 273-274° (lit.<sup>12</sup> mp 274°); ir ( $\text{CHCl}_3$ ), 1775 and 1737  $\text{cm}^{-1}$  (anhydride  $\text{C=O}$ , absorbance ratio  $A_{1737}/A_{1775} = 0.86$ ). Following a previously described procedure,<sup>13</sup> the anhydride 33 was dissolved in methanolic KOH and this solution was treated simultaneously with MeOH solutions of  $(\text{MeO})_2\text{SO}_2$  and of KOH. The neutral product was

crystallized from MeOH to separate the diester 35 as white needles, mp 100-101° (lit.<sup>13</sup> mp 102°); ir (CCl<sub>4</sub>), 1728 cm<sup>-1</sup> (ester C=O); uv max (95% EtOH), 299 mμ (ε 3500); nmr (CCl<sub>4</sub>), δ 7.2-8.0 (6H, m, aryl CH) and 3.81 (6H, s, OCH<sub>3</sub>). Alternatively, mixtures of the esters could be analyzed by glpc (Silicone fluid No. 710, on Chromosorb P) with the following retention times being observed for the esters: 37, 13.8 min; 39, 15.0 min; and 35, 31.8 min.

The crude product from the reduction contained (nmr analysis of the diesters) ca. 90% of acid 36 and ca. 10% of acid 38. A 1.289-g aliquot of this mixture was fractionally recrystallized from MeOH to separate 451 mg of the pure (nmr analysis of diester) acid 36 as white prisms, mp 218-223° dec (dependent on rate of heating); ir (KBr pellet), 1720, 1695 (carboxyl C=O), 1665, and 1630 cm<sup>-1</sup> (C=C); uv (95% EtOH), end absorption with ε 1330 at 210 mμ; nmr (pyridine-d<sub>5</sub>), δ 13.0 (2 H, s, OH), 5.7 - 6.4 (4 H, m, vinyl CH), 4.4-4.9 (2 H, m, CHCO<sub>2</sub>R), and 2.5-2.8 (4H, m, allylic CH<sub>2</sub>).

Anal. Calcd for C<sub>12</sub>H<sub>12</sub>O<sub>4</sub>: C, 65.44; h, 5.49.

Found: C, 65.53; H, 5.53.

To a cold (-33°) solution of NaNH<sub>2</sub>, from 430 mg (18.7 mg-atom) of Na and 180 ml of liquid NH<sub>3</sub>, was added 1.54 g (7.00 mmol) of a mixture of diacids (ca. 80% of 36 and 20% of 38). After the resulting gray-green suspension had been stirred at -33° for 1.5 hr, a solution of 100 mg (5.6 mmol) of H<sub>2</sub>O in THF was added, dropwise and with stirring during

1.5 hr. Then 5 ml of  $H_2O$  was added, the  $NH_3$  was allowed to evaporate, and a solution of the residue in 50 ml of cold ( $0^\circ$ )  $H_2O$  was filtered and acidified with cold aqueous 12 M HCl. The crystalline acid that separated was collected as 1.252 g of tan solid containing (nmr analysis of diesters) ca. 67% of diacid 38 and ca. 33% of diacid 36. Fractional recrystallization of an 836-mg aliquot of this mixture from MeOH separated 230 mg of the pure (nmr analysis of the diester) diacid 38 as white prisms, mp  $211-215^\circ$  dec. (dependent on rate of heating); ir (KBr pellet), 1710 and  $1685\text{ cm}^{-1}$  (carboxyl C=O); uv (95% EtOH), end absorption with  $\epsilon$  1320 at 210 m $\mu$ ; nmr (pyridine- $d_5$ ),  $\delta$  11.9 (2H, broad, OH), 5.8-6.5 (4H, m, vinyl CH), 3.9-4.3 (2H, m,  $CHCO_2R$ ), and 2.5-2.9 (4 H, m, allylic  $CH_2$ ).

Anal. Calcd for  $C_{12}H_{12}O_4$ : C, 65.44; H, 5.49.

Found: C, 65.46; H, 5.49.

A mixture of approximately equal amounts of the diacids 36 and 38 was esterified with excess ethereal  $CH_2N_2$  and this crude neutral product was chromatographed on silica gel with an  $Et_2O$ -PhH eluent (1:49 v/v). The initial chromatographic fractions were recrystallized from  $Et_2O$ -hexane mixtures to separate the pure diester 37 as white needles, mp  $71-72.5^\circ$ ; ir ( $CCl_4$ ), 1740 (ester C=O) and  $1665\text{ cm}^{-1}$  (weak, C=C); uv (95% EtOH), end absorption with  $\epsilon$  1090 at 210 m $\mu$ ; nmr ( $CCl_4$ ),  $\delta$  5.5-6.1 (4 H, m, vinyl CH), 3.5-3.9 (8 H, m,  $CHCO_2R$  with a  $CH_3O$  singlet at 3.67), and 2.5-2.8 (4 H, m, allylic



CH<sub>2</sub>); mass spectrum, m/e (rel. intensity), 248 (M<sup>+</sup>, 4), 216 (28), 188 (26), 156 (10), 129 (100), and 128 (25).

Anal. Calcd for C<sub>14</sub>H<sub>16</sub>O<sub>4</sub>: C, 67.73; H, 6.50.

Found: C, 67.49; H, 6.56.

The later chromatographic fractions were recrystallized from Et<sub>2</sub>O-hexane to separate the pure diester 39 as white prisms, mp 124-126°; ir (CCl<sub>4</sub>), 1740 (ester C=O) and 1665 cm<sup>-1</sup> (C=C); uv (95% EtOH), end absorption with ε 1050 at 210 mμ; nmr (CCl<sub>4</sub>), δ 5.5-6.1 (4 H, m, vinyl CH), 3.4-3.8 (8 H, m, CHCO<sub>2</sub>R with a CH<sub>3</sub>O singlet at 3.57), and 2.5-3.0 (4 H, m, allylic CH<sub>2</sub>); mass spectrum, m/e (rel. intensity), 248 (M<sup>+</sup>, 5), 216 (7), 189 (16), 188 (14), 129 (100), and 128 (21).

Anal. Calcd for C<sub>14</sub>H<sub>16</sub>O<sub>4</sub>: C, 67.73; H, 6.50.

Found: C, 67.65; H, 6.58.

After a suspension of 162 mg (0.74 mmol) of the anti-diacid 36 in 5 ml of CH<sub>2</sub>Cl<sub>2</sub> containing 163 mg (0.79 mmol) of dicyclohexylcarbodiimide had been stirred at 25° for 75 min, the mixture was filtered to remove dicyclohexylurea. The yellow filtrate was concentrated under reduced pressure and triturated with pentane to leave 163 mg of the crude syn-anhydride 40 as a yellow solid, ir (CHCl<sub>3</sub>), 1804 and 1762 cm<sup>-1</sup> (anhydride C=O). This crude product was stirred at 25° with 2 ml of DME and 1 ml of aqueous 3 M HCl for 10 hr and then concentrated under reduced pressure and washed with H<sub>2</sub>O. The residual red-brown solid (134 mg) was combined with

additional material obtained from extraction of the aqueous washings with  $\text{CH}_2\text{Cl}_2$  and the total crude product (154 mg) was esterified with excess ethereal  $\text{CH}_2\text{N}_2$ . After this mixture had been filtered and concentrated, the residue amounted to 121 mg of yellow solid with ir and nmr absorption corresponding to the syn-diester 39. Analysis (glpc, Silicone, fluid, No. 710, on Chromosorb P) indicated the presence of the syn-diester 39 (ret time 13.3 min) accompanied by four minor, unidentified impurities (7.8, 12.1, 15.6, and 24.2 min). After an aliquot of the crude esterified product had been mixed with a known amount of internal standard (n- $\text{C}_{24}\text{H}_{50}$ , ret. time 29.5 min), the calculated (glpc) yield of the syn-diester 39 was 31%.<sup>14</sup> A collected (glpc) sample of the peak corresponding in retention time to the syn-diester 39 was identified with an authentic sample by comparison of ir spectra. In another comparable experiment, the crude syn-anhydride 40 was partially purified by adding pentane to a  $\text{CHCl}_3$  solution of the crude anhydride and by sublimation under reduced pressure at  $85^\circ$ . This partially purified solid anhydride 40 exhibited nmr peaks ( $\text{CDCl}_3$ ) at  $\delta$  6.0-6.3 (ca. 4 H, m, vinyl CH), 3.7-4.2 (ca. 2H, m, allylic CH-CO), and 2.5-2.9 (ca. 4 H, m, allylic  $\text{CH}_2$ ) with ir absorption ( $\text{CHCl}_3$ ) at 1804 and  $1762\text{ cm}^{-1}$  (anhydride C=O, absorbance ratio,  $A_{1762}/A_{1804} = 1.69$ ). As a control experiment to demonstrate that the anti-acid 36 was not epimerized by the hydrolysis conditions, a suspension of 105 mg (0.48 mmol)

of the anti-acid 36 in 2 ml of DME and 1 ml of aqueous 3 M HCl was stirred for 10 hr at 25° and then subjected to the previously described isolation and esterification procedures. The final neutral product obtained was 101 mg (85%) of the anti-diester 37, mp 71-71.5°, that was identified with an authentic sample by glpc analysis and comparison of ir spectra.

A suspension of 119 mg (0.54 mmol) of the syn-diacid 38 in 5 ml of CH<sub>2</sub>Cl<sub>2</sub> containing 125 mg (0.61 mmol) of dicyclohexylcarbodiimide was stirred at 25° for 75 min and then subjected to the previously described isolation procedure. The crude syn-anhydride 40 (121 mg of yellow solid with ir absorption corresponding to the previously described sample) was hydrolyzed at 25° for 10 hr with 2 ml of DME and 1 ml of aqueous 3 M HCl and subjected to the previously described isolation and esterification procedure. The crude neutral product (95 mg of yellow solid) contained (glpc) the syn-diester 39 accompanied by the same minor impurities noted in the preparation from the anti-acid. After an aliquot of this neutral product had been mixed with a known amount of internal standard (n-C<sub>24</sub>H<sub>50</sub>), the calculated (glpc) yield of the syn-diester 39 was 25%.<sup>14</sup>

#### Reductive Methylation of the Acid 41

After a solution of 1.036 g (6.82 mmol) of the acid 41 in 10 ml of THF had been added to 50 ml of liquid NH<sub>3</sub>, the resulting white suspension was treated, portion wise and with

stirring, with 167 mg (24.1 mg-atom) of Li. The reaction mixture changed successively from a white suspension to a colorless solution, then to a yellow solution, and finally to a blue solution. This cold ( $-33^{\circ}$ ) blue solution was treated with 4.56 g (32.1 mmol) of MeI and the resulting pale yellow solution was stirred at  $-33^{\circ}$  for 90 min and then treated with 2 ml of  $\text{H}_2\text{O}$ . After the  $\text{NH}_3$  had evaporated, the residue was partitioned between cold ( $0^{\circ}$ ) dilute aqueous HCl and  $\text{CH}_2\text{Cl}_2$  and the organic phase was washed with aqueous NaCl, dried, and concentrated. The residual yellow oil was esterified with excess ethereal  $\text{CH}_2\text{N}_2$  and this resulting solution was washed with aqueous  $\text{NaHCO}_3$ , dried, and concentrated. An aliquot of the residual neutral product (1.078 g of pale orange liquid) was mixed with a known weight of internal standard (naphthalene) and analyzed by glpc (LAC-728 on Chromosorb P). The product contained ester 43 (ret. time 8.0 min, 47% yield), naphthalene (19.0 min), and ester 42 (25.2 min, 27% yield). The same general procedure was repeated with 1.059 g (7.02 mmol) of acid 41, 10 ml of THF, 50 ml of liquid  $\text{NH}_3$ , 528 mg (23.0 mg-atom) of Na, and 4.56 g (32.1 mmol) of MeI. After following the same isolation and analysis procedures, the yields of esters 43 and 42 were 31% and 41%, respectively. Thus, the demethoxylation side reaction leading to by-product 43 is less serious when the reduction is effected with Na rather than Li.

To identify the reaction products, the reduction was

repeated with 10.0 g (69.7 mmol) of acid 41, 300 ml of liquid  $\text{NH}_3$ , 75 ml of THF, 1.584 g (226 mg-atom) of Li, and 34.2 g (240 mmol) of MeI. After esterification with  $\text{CH}_2\text{N}_2$ , the crude neutral product (11.62 g) was fractionally distilled through a 15-cm Vigreux column. From the early fractions [3.49 g, bp 85-86° (18 mm)] containing (glpc) mainly the ester 43, a pure sample of the ester 43 was collected as a colorless liquid,  $n_D^{25}$  1.4732; ir ( $\text{CCl}_4$ ), 1734  $\text{cm}^{-1}$  (ester C=O); uv (95% EtOH), end absorption with  $\epsilon$  1400 at 210 m $\mu$ ; nmr ( $\text{CCl}_4$ ),  $\delta$  5.5-6.0 (4 H, m, vinyl CH), 3.60 (3H, s,  $\text{OCH}_3$ ), 2.4-2.8 (2 H, m, allylic  $\text{CH}_2$ ), and 1.26 (3H, s,  $\text{CH}_3$ ); mass spectrum, m/e (rel. intensity), 152 ( $\text{M}^+$ , 4), 93 (100), 92 (27), 91 (38), 77 (41), and 39 (14).

Anal. Calcd for  $\text{C}_9\text{H}_{12}\text{O}_2$ : C, 71.02; H, 7.95. Found: C, 71.00; H, 7.95.

After separation of an intermediate distillation fraction [1.35 g, bp 86-121° (18 min), a mixture of 42 and 43, the final distillation fraction [4.09 g, bp 121-143° (18 mm)] contained (glpc) mainly the ester 42 accompanied (ir and nmr analysis) by some of the acid corresponding to ester 43. This fraction was re-extracted with aqueous  $\text{NaHCO}_3$  and redistilled to separate 1.945 (15%) of the ester 42 as a colorless liquid, bp 113-116° (16 min).<sup>15</sup> A collected (glpc) sample of the ester 42 was obtained as a colorless liquid,  $n_D^{25}$  1.4829; ir ( $\text{CCl}_4$ ), 1740 (ester C=O), 1690 (enol ether C=C), and 1650  $\text{cm}^{-1}$  (C=C); nmr ( $\text{CCl}_4$ ),  $\delta$

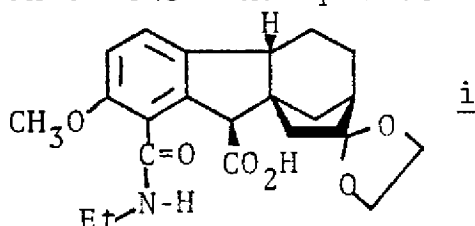
5.2-5.9 (2 H, m, vinyl CH), 4.64 (1H, t,  $J = 3$  Hz, enol ether vinyl CH), 3.59 (3H, s,  $\text{OCH}_3$ ), 3.52 (3H, s,  $\text{OCH}_3$ ), 2.6-2.9 (2H, m, allylic  $\text{CH}_2$ ), and 1.33 (3H, s,  $\text{CH}_3\text{-C}$ ); uv mix (95% EtOH), 272 m $\mu$  ( $\epsilon$  53) with intense end absorption ( $\epsilon$  2360 at 210 m $\mu$ ); mass spectrum, m/e (rel. intensity), 182 ( $\text{M}^+$ , 8), 123 (100), 108 (25), and 91 (18).

Anal. Calcd for  $\text{C}_{10}\text{H}_{14}\text{O}_3$ : C, 65.91; H, 7.74.

Found: C, 65.65; H, 7.64.

## References and Notes

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2. (a) H. O. House, T. M. Bare, and W. E. Hanners, *J. Org. Chem.*, **34**, 2209 (1969); (b) H. O. House, W. E. Hanners, and E. J. Racah, *ibid.*, **37**, 985 (1972).
3. Baker and Goudie [A. J. Baker and A. C. Goudie, *J. Chem. Soc., Chem. Comm.*, 951 (1972)] have reported hydrolyzing the amido acid 1 to the corresponding diacid via the nitrosoamide in 80% yield. In the case of 24, only 45% of pure diacid 1 could be obtained. Byproducts, possibly from nitrosation of the aromatic ring, made purification of the final product difficult.



4. (a) W. G. Dauben and W. W. Epstein, *J. Org. Chem.*, **24**, 1595 (1959); (b) F. H. Marquardt, *J. Chem. Soc. (B)*, 1242 (1966); (c) C. Fayat and A. Foucaud, *C. R. Acad. Sci., Ser. B*, **263**, 860 (1966); (d) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen, England, 1968, pp. 128-131; (e) N. B. Colthup, L. H. Daly, and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy," 2d ed., Academic Press, New York, N. Y., 1975, pp. 297-298.
5. All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated  $\text{MgSO}_4$  was employed as a drying agent. The ir spectra was determined with a Perkin Elmer, Model 257, infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary, Model 14, or a Perkin Elmer, Model 202, recording spectrophotometer. The proton nmr spectra were determined at 60 MHz with a Varian, Model A-60 or Model T-60-A, nmr spectrometer and the  $^{13}\text{C}$  nmr spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in  $\delta$  values (ppm) relative to a  $\text{Me}_4\text{Si}$  internal standard. The mass spectra were obtained with an Hitachi (Perkin Elmer), Model RMU-7, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

6. O. H. Wheeler and I. Lerner, J. Am. Chem. Soc., 78, 63 (1956).
7. (a) S. Dev, J. Indian Chem. Soc., 33, 769 (1956);  
(b) H. O. House and R. Darms, unpublished results.
8. W. G. Dauben and J. W. Collette, J. Am. Chem. Soc., 81, 967 (1959).
9. The esterification procedure of J. L. Marshall, K. C. Erickson, and T. K. Folsom [Tetrahedron Lett., 4011 (1970)] was used.
10. This slow addition of a solution of the diacid was necessary to minimize formation of a by-product resulting from protonation of the initially formed carbanion before the  $\text{CH}_3\text{I}$  was added.
11. This compound was first characterized in these laboratories by Dr. Roger C. Strickland.
12. C. Graebe and E. Gfeller, Ber., 25, 652 (1892).
13. T. A. Geissman and V. Tulagin, J. Am. Chem. Soc., 66, 716 (1944).
14. Since both esters 37 and 39 undergo partial decomposition under the conditions of our glpc analysis, we regard these yields as minimum values.
15. The initial characterization of this ester was performed in our laboratories by Dr. Thomas M. Bare.



## CHAPTER III

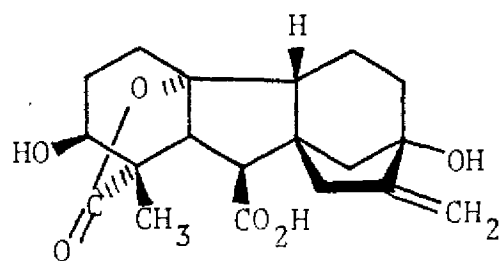
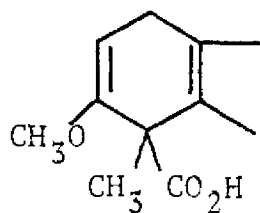
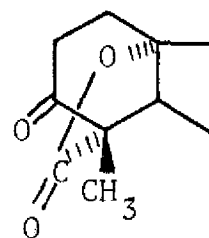
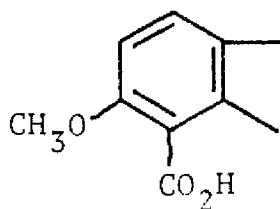
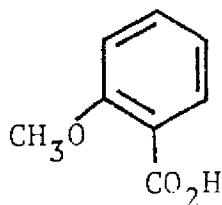
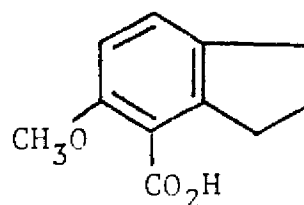
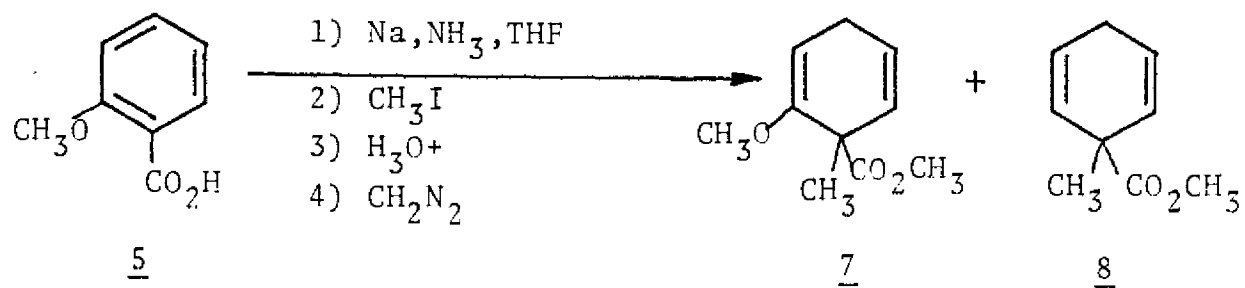
STUDIES ON THE SYNTHESIS OF THE GIBBERELLIN  
A RING LACTONE SYSTEMDiscussion

As part of an investigation of the synthesis of the A ring lactone of certain gibberellins [e.g. gibberellin A<sub>1</sub> (1)], the conversion of the acid 2 to the keto lactone 3 was studied on simple systems. The acid 2 is readily available from the corresponding aromatic acid 4 by the method of Lowenthal and coworkers.<sup>1</sup> The two systems used in this study were derived from the aromatic acids 5 and 6.

The aromatic acid 5 was converted to the mixture of esters 7 and 8 as previously described.<sup>2</sup> Hydrolysis of the enol ether 7 gave the keto ester 9. The keto ester 9 was epoxidized with m-chloroperbenzoic acid in CHCl<sub>3</sub> to give a mixture of epoxides 10 and 11, each of which could be converted to a different iodo hydrin upon treatment with NaI in a mixture of acetic and propionic acids. The relative stereochemistry in compounds 10-13, and the location of the iodo and hydroxyl groups in compounds 12 and 13 remains unknown. No further work was done on this system.

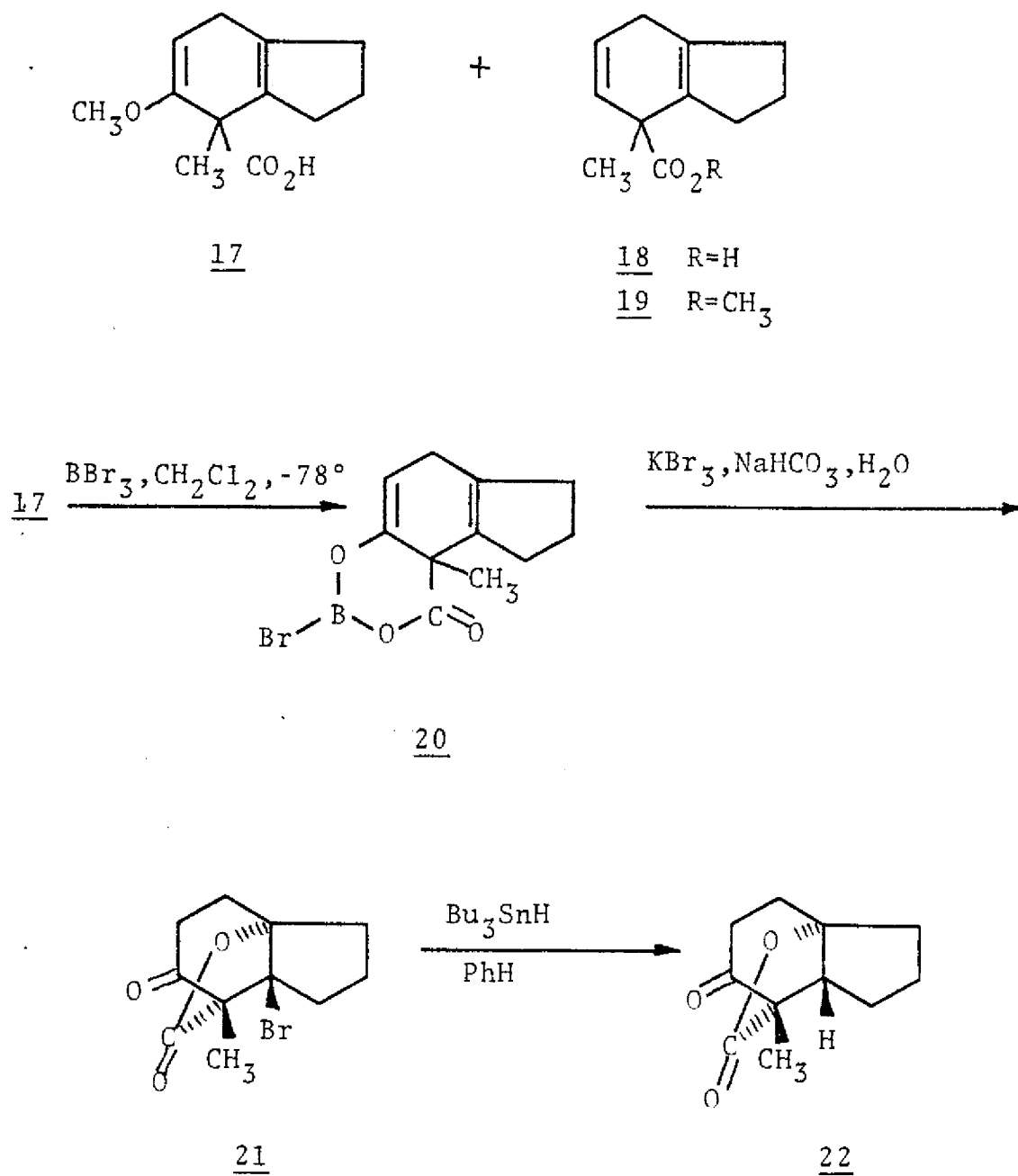
The aromatic acid 6, prepared from the methoxy indanone 14 as outlined in scheme I, was reduced and methylated to

Scheme I

123456



## Scheme I (cont.)



give a mixture of the acids 17 and 18. Acid 18 was characterized as the methyl ester 19. The reduced acid 17 was converted to the bromolactone 21 by first treating it with one equivalent of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ$  to form presumably the cyclic borane ester 20, followed by lactonization with an aqueous solution of  $\text{KBr}_3$  and  $\text{NaHCO}_3$ . The crude bromolactone 21 was reduced with  $n\text{-Bu}_3\text{SnH}$  to give the keto lactone 22 in 65% isolated yield from acid 17. The keto lactone 22 had infrared and nmr spectra identical to those of a sample prepared by an alternate route;<sup>3</sup> the reduction of the bromolactone 21, therefore, takes place with retention of configuration.

### Experimental Section<sup>4</sup>

#### Preparation of the Keto Ester 9

Following a previously described<sup>2</sup> procedure, a solution of 30.9g (0.204 mol) of acid 5 in 125 ml of THF was added to 900 ml of cold (ca.  $-78^\circ$ ) liquid  $\text{NH}_3$ . The resulting suspension was allowed to warm to  $-33^\circ$  and 14.7 g (0.64 g-atom) of Na was added, portion wise and with stirring. While the resulting blue solution was maintained at  $-33^\circ$ , 92 g (0.64 mol) of MeI was added, dropwise with stirring and cooling, causing the reaction solution to change from blue to red to colorless. After the  $\text{NH}_3$  had been allowed to evaporate, the residue was diluted with 200 ml of  $\text{H}_2\text{O}$ , concentrated under reduced pressure, treated with 250 ml of

$\text{CH}_2\text{Cl}_2$ , and acidified by addition, with cooling and stirring, of cold aqueous 1 M  $\text{HCl}$ . The combined  $\text{CH}_2\text{Cl}_2$  layer and the  $\text{CH}_2\text{Cl}_2$  extract of the aqueous phase were washed with aqueous  $\text{NaCl}$ , dried, concentrated, and esterified with excess ethereal diazomethane. After the resulting product had been partitioned between  $\text{Et}_2\text{O}$  and aqueous  $\text{NaHCO}_3$ , the organic layer was dried, concentrated and distilled through a 25-cm Vigreux column. After separation of the lowest boiling fraction containing (glpc, LAC-728 on Chromosorb P) 7.14 g (23%) of the crude ester 8 (ret. time 5.8 min), bp  $80-86^\circ$  (13 mm),  $n_D^{25}$  1.4715 [lit.<sup>2</sup> bp  $85-86^\circ$  (18 mm),  $n_D^{25}$  1.4732], the next fraction, 4.17 g of colorless liquid, bp  $86-110^\circ$  (13 mm),  $n_D^{25}$  1.4750, contained (glpc) a mixture of esters 8 (5.8 min) and 7 (16.2 min). Subsequent fractions contained (glpc) 15.1 g (41%) of practically pure ester 7, bp  $95-113^\circ$  (5-13 mm),  $n_D^{25}$  1.4833-1.4852 [lit.<sup>2</sup> bp  $113-116^\circ$  (16 mm),  $n_D^{25}$  1.4829].

A cold ( $0^\circ$ ) solution of 5.29 g (29.0 mmol) of the ester 7 in 30 ml of THF was treated with 4 ml (48 mmol) of aqueous 12 M  $\text{HCl}$  and the mixture was stirred for 1 hr while it was allowed to warm to  $25^\circ$ . After the mixture had been diluted with  $\text{H}_2\text{O}$  and concentrated under reduced pressure, it was partitioned between  $\text{H}_2\text{O}$  and  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with aqueous  $\text{NaCl}$ , dried, and concentrated to leave 4.95 g of the crude keto ester 9 as a pale yellow liquid. Chromatography on silica gel with an  $\text{Et}_2\text{O}$ -hexane

eluent (1:9 v/v) afforded 3.89 g (80%) of the keto ester 9 as a colorless liquid,  $n_D^{25}$  1.4707, that exhibited a single peak (ret. time 15.5 min) on glpc analysis (LAC-728 on Chromosorb P). A collected (glpc) sample of the keto ester 9,  $n_D^{25}$  1.4724, was used for characterization; ir ( $\text{CCl}_4$ ), 1745 (ester C=O), 1720 (C=O) and 1655  $\text{cm}^{-1}$  (weak, C=C); uv (95% EtOH), end absorption ( $\epsilon$  1100 at 210 nm) with a maximum at 287 nm ( $\epsilon$  34); nmr ( $\text{CCl}_4$ ),  $\delta$  5.5-6.1 (2H, m, vinyl CH), 3.67 (3H, s,  $\text{OCH}_3$ ), 2.2-2.9 (4H, m, allylic  $\text{CH}_2$  and  $\text{CH}_2\text{CO}$ ), and 1.32 (3H, s,  $\text{CH}_3$ ); mass spectrum, m/e (rel. intensity), 168 ( $\text{M}^+$ , 39), 140 (36), 126 (100), 125 (40), 112 (34), 111 (60), 109 (71), 108 (27), 96 (44), 95 (53), 81 (65), 79 (33), 67 (56), 53 (39), 43 (23), 41 (61), and 39 (54).

Anal. Calcd for  $\text{C}_9\text{H}_{12}\text{O}_3$ : C, 64.27; H, 7.19.

Found: C, 64.30; H, 7.20.

#### Preparation of the Epoxides 10 and 11

A solution of 2.84 g (16.9 mmol) of the keto ester 9 and 3.70 g of a reagent containing 18.2 mmol of m-chloroperbenzoic acid in 50 ml of  $\text{CHCl}_3$  (EtOH free) was refluxed for 5 hr and then allowed to stand for 9 hr at 25°. After the mixture had been partitioned between  $\text{CH}_2\text{Cl}_2$  and aqueous  $\text{Na}_2\text{SO}_3$ , the organic layer was washed successively with aqueous  $\text{NaHCO}_3$  and with aqueous NaCl and then dried and concentrated. The residual yellow liquid (4.0 g) was chromatographed on silica gel with an EtOAc-hexane eluent

(1:3 v/v). The early chromatography fractions contained 1.708 g (55%) of the epoxide 10 as a colorless liquid,  $n_D^{25}$  1.4710. Short-path distillation (0.3 mm with an 85° bath) afforded the pure epoxide 10,  $n_D^{25}$  1.4703; ir (CCl<sub>4</sub>), 1760 (ester C=O) and 1720 cm<sup>-1</sup> (C=O); uv max (95% EtOH), 283 nm ( $\epsilon$  36); nmr (CCl<sub>4</sub>),  $\delta$  3.73 (3H, s, OCH<sub>3</sub>), 3.1-3.5 (2H, m, epoxide CH-O), 2.0-2.6 (4H, m, CH<sub>2</sub>), and 1.42 (3H, s, CH<sub>3</sub>); mass spectrum, m/e (rel. intensity), 184 (M<sup>+</sup>, 1), 128 (32), 125 (32), 124 (28), 97 (84), 84 (30), 82 (30), 69 (71), 68 (30), 59 (46), 56 (50), 55 (65), 43 (33), 41 (100), and 39 (79).

Anal. Calcd for C<sub>9</sub>H<sub>12</sub>O<sub>4</sub>: C, 58.69; H, 6.57.

Found: C, 58.70; H, 6.59.

The later chromatography fractions contained 930 mg (30%) of the epoxide 11 as a colorless liquid,  $n_D^{25}$  1.4751. Short-path distillation (0.3 mm with an 85° bath) afforded the pure epoxide 11,  $n_D^{25}$  1.4752; ir (CCl<sub>4</sub>), 1745 (ester C=O) and 1720 cm<sup>-1</sup> (C=O); uv max (95% EtOH), 285 nm ( $\epsilon$  25), nmr (CCl<sub>4</sub>),  $\delta$  3.75 (3H, s, OCH<sub>3</sub>), 3.0-3.5 (2H, m, epoxide CH-O), 1.9-2.8 (4H, m, CH<sub>2</sub>) and 1.38 (3H, s, CH<sub>3</sub>); mass spectrum, m/e (rel. intensity), 184 (M<sup>+</sup>, 1), 128 (25), 125 (28), 124 (23), 110 (28), 101 (29), 97 (78), 85 (32), 69 (55), 68 (25), 59 (41), 58 (24), 56 (43), 55 (54), 43 (32), 41 (100), and 39 (61).

Anal. Calcd for C<sub>9</sub>H<sub>12</sub>O<sub>4</sub>: C, 58.69; H, 6.57.

Found: C, 58.84; H, 6.61.



### Preparation of the Iodohydrins 12 and 13

Following a general procedure described previously,<sup>5</sup> a solution of 216 mg (1.17 mmol) of the epoxide 10, 445 mg (2.97 mmol) of NaI, 123 mg (1.5 mmol) of NaOAc, and 1.0 ml of HOAc in 2.0 ml of propionic acid was stirred at 25° for 2.5 hr. After the mixture had been partitioned between Et<sub>2</sub>O and an aqueous solution of NaHCO<sub>3</sub> and NaHSO<sub>3</sub>, the organic layer was washed with aqueous NaCl, dried, and concentrated. The residual liquid (331 mg) crystallized from a CCl<sub>4</sub>-hexane mixture as 279 mg of colorless solid, mp 93-94°. Recrystallization separated 233 mg (65%) of the iodohydrin 12 as colorless prisms, mp 96-97°. Further recrystallization gave the iodohydrin 12, mp 97-99°; ir (CHCl<sub>3</sub>), 3570, 3410 (OH), 1740 (ester C=O), and 1712 cm<sup>-1</sup> (C=O); uv max 95% EtOH), 260 nm ( $\epsilon$  620); nmr (CDCl<sub>3</sub>),  $\delta$  4.2-4.7 (2H, m, CH-O, CHI), 3.78 (3H, s, OCH<sub>3</sub>), 2.9-3.1 (1H, m, OH, exchanged with D<sub>2</sub>O), 1.9-2.9 (4H, m, CH<sub>2</sub>), and 1.43 (3H, s, CH<sub>3</sub>); mass spectrum, m/e (rel. intensity), 312 (M<sup>+</sup>, <1), 185 (41), 153 (36), 125 (30), 107 (45), 97 (32), 83 (55), 79 (40), 71 (32), 69 (32), 59 (45), 56 (28), 55 (99), 54 (25), 42 (30), 41 (100), and 39 (64).

Anal. Calcd for C<sub>9</sub>H<sub>13</sub>IO<sub>4</sub>: C, 34.64; H, 4.20; I, 40.66. Found: C, 34.58; H, 4.26; I, 40.71.

The same procedure was employed with 142 mg (0.77 mmol) of the epoxide 11, 239 mg (1.59 mmol) of NaI, 48 mg (0.59 mmol) of NaOAc, 0.6 ml of HOAc, and 1.0 ml of propionic

acid with a reaction time of 3 hr at 25°. The crude neutral product (199 mg of colorless solid, mp 79-95°) was triturated with pentane and recrystallized from a PhH-hexane mixture to separate 121 mg (50%) of the iodohydrin 13 as a colorless prism, mp 106-107°; ir (CHCl<sub>3</sub>), 3500 (broad, OH), 1735 (shoulder, ester C=O), 1718 (shoulder), and 1708 cm<sup>-1</sup> (C=O); uv max (95% EtOH), 261 nm ( $\epsilon$  640); nmr (CDCl<sub>3</sub>),  $\delta$  4.4-4.9 (1H, m, CH-O or CH-I), 3.75 (3H, s, OCH<sub>3</sub>), 3.59 (1H, OH, exchanged with D<sub>2</sub>O), 3.47 (1H, d, J = 11 Hz, CH-O or CH-I), 2.1-2.9 (4H, m, CH<sub>2</sub>), and 1.53 (3H, s, CH<sub>3</sub>); mass spectrum, m/e (rel. intensity), 294 (4), 185 (44), 153 (31), 147 (28), 127 (28), 125 (30), 97 (29), 85 (62), 83 (60), 71 (30), 69 (30), 59 (45), 56 (29), 55 (94), 43 (68), 41 (100), and 39 (60).

Anal. Calcd for C<sub>9</sub>H<sub>13</sub>IO<sub>4</sub>: C, 34.64; H, 4.20; I, 40.66. Found: C, 34.69; H, 4.24; I, 40.69.

#### Preparation of the Acid 6

Several modifications in the previously described<sup>6</sup> procedure for the hydroxy acid 16 were found desirable. Thus, reduction of 23.7 g (1.46 mmol) of 6-methoxyindan-1-one (14) with LiAlH<sub>4</sub> (2.6 g or 68 mmol) in 250 ml of THF gave 22.8 g (95%) of 6-methoxyindan-1-ol (15), mp 45.5-46° (lit.<sup>6</sup> mp 46-47.5°). Reaction of a suspension of 12.3 g (75 mmol) of this alcohol with 194 mmol of n-BuLi in 460 ml of hexane at 25° for 12 hr yielded a red suspension of the lithium reagent. This suspension was cooled to -78° and stirred under

an atmosphere of  $\text{CO}_2$  for 45 min. The usual isolation procedure<sup>6</sup> yielded 14.7 g (94%) of the hydroxy acid 16, mp 155-157° dec (lit.<sup>6</sup> mp 150-151° to 160-161°, dec).

A suspension of 3.82 g (18.4 mmol) of the acid 16 in 40 ml of THF and 10 ml of HOAc containing 0.4 ml of aqueous 70%  $\text{HClO}_4$  was hydrogenated at 25° and 1 atm over 300 mg of 5% Pd-C catalyst. After 2 hr the  $\text{H}_2$  uptake (21.4 mmol) was complete and the reaction mixture was filtered and concentrated. A solution of the residual material in  $\text{CH}_2\text{Cl}_2$  was washed with  $\text{H}_2\text{O}$ , dried, and concentrated to leave 3.40 g of the solid acid 6, mp 135-138°. Recrystallization from a hexane- $\text{CH}_2\text{Cl}_2$  mixture afforded 3.14 g (89%) of crops of the acid 6 as colorless prisms melting within the range 135-139°. Another recrystallization gave the pure acid 6, mp 138-139°; ir ( $\text{CHCl}_3$ ), 3250 (carboxyl OH), 1735 (shoulder), and 1725  $\text{cm}^{-1}$  (carboxyl C=O); uv max (95% EtOH), 294 nm ( $\epsilon$  2700) with intense end absorption ( $\epsilon$  18,000 at 210 nm); nmr ( $\text{CDCl}_3$ ),  $\delta$  7.31 (1H, d,  $J$  = 8.5 Hz, aryl CH), 6.82 (1H, d,  $J$  = 8.5 Hz, aryl CH), 3.96 (3H, s,  $\text{OCH}_3$ ), 3.31 (2H, t,  $J$  = 7.5 Hz, benzylic  $\text{CH}_2$ ), 2.86 (2H, t,  $J$  = 7.5 Hz, benzylic  $\text{CH}_2$ ), and 1.7-2.4 (2H, m,  $\text{CH}_2$ ); mass spectrum,  $m/e$  (rel. intensity), 192 ( $\text{M}^+$ , 62), 174 (100), 159 (25), 117 (30), 116 (73), 115 (53), 103 (30), 77 (35), and 51 (25).

Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{O}_3$ : C, 68.73; H, 6.29.  
Found: C, 68.87; H, 6.30.

### Preparation of the Acid 17

A solution of 1.51 g (7.87 mmol) of the acid 6 in 10 ml of THF was added, dropwise and with stirring, to a refluxing solution of 530 mg (23 mg-atom) of Na in 250 ml of liquid  $\text{NH}_3$ . After the resulting blue solution had been stirred at  $-33^\circ$  for 15 min, it was cooled in a dry ice-acetone bath and treated with 4.5 g (32 mmol) of  $\text{CH}_3\text{I}$ . The  $\text{NH}_3$  was allowed to evaporate from the resulting colorless solution and the residue was acidified with dilute aqueous  $\text{HCl}$ , the aqueous phase was saturated with  $\text{NaCl}$ , and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  extract was dried and concentrated to leave 1.54 g of pale yellow solid that contained (nmr analysis) ca. 75% of the acid 17 and ca. 25% of the acid 18. Recrystallization from an EtOAc-hexane mixture separated 748 mg (46%) of the acid 17, mp  $125-128^\circ$  dec. An additional recrystallization gave the pure acid 17 as colorless plates, mp  $126-129^\circ$  dec; ir ( $\text{CHCl}_3$ ), 2800-3200 (associated OH), 1708, 1695 (carboxyl  $\text{C=O}$ ), and  $1658\text{ cm}^{-1}$  ( $\text{C=C}$ ); uv (95% EtOH), end absorption with  $\epsilon$  3700 at 210 nm; nmr ( $\text{CDCl}_3$ ),  $\delta$  11.5 (1H, s, OH), 4.83 (1H, t,  $J = 3.5\text{ Hz}$ , vinyl CH), 3.57 (3H, s,  $\text{OCH}_3$ ) 1.6-2.9 (8H, m,  $\text{CH}_2$ ), and 1.41 (3H, s,  $\text{CH}_3$ ); mass spectrum, m/e (rel. intensity), 164 (48), 149 (21), 91 (22), and 44 (100).

Anal. Calcd for  $\text{C}_{12}\text{H}_{16}\text{O}_3$ : C, 69.21; H, 7.74.  
Found: C, 69.24; H, 7.76.

In a similar experiment, a solution of 841 mg (4.38 mmol) of the acid 6 in 20 ml of THF was added to a cold (-33°) solution of 113 mg (19 mg-at) of Li in 100 ml of NH<sub>3</sub>. After the resulting mixture had been stirred at -33° for 15 min, it was cooled in a dry ice bath and 9.1 g (64 mmol) of CH<sub>3</sub>I was added. The mixture was allowed to warm to -33°, the NH<sub>3</sub> was allowed to evaporate, and the previously described isolation procedure was followed to separate 800 mg of crude acidic product containing (nmr analysis) ca. 45% of the acid 17 and ca. 55% of the acid 18. A solution of this mixture in 10 ml of THF and 2 ml of aqueous 6 M HCl was stirred at 25° for 30 min to hydrolyze the enol ether 17 and decarboxylate the corresponding keto acid. The resulting mixture was partitioned between aqueous NaHCO<sub>3</sub> and Et<sub>2</sub>O, and the aqueous phase was acidified with concentrated HCl and extracted with Et<sub>2</sub>O. After this extract had been dried and concentrated, the crude residual acid 18 (418 mg) was esterified with excess ethereal CH<sub>2</sub>N<sub>2</sub>. The resulting Et<sub>2</sub>O solution was washed with aqueous NaHCO<sub>3</sub>, dried, and concentrated to leave 398 mg of the crude ester 19 as a pale yellow liquid containing (glpc, silicone DC-710 on chromosorb P) the ester 19 (ret. time 7.0 min) and several minor unidentified impurities (3.0 min, 8.4 min). A collected (glpc) sample of the ester 19 was obtained as a colorless liquid, n<sup>25</sup><sub>D</sub> 1.5000; ir (CCl<sub>4</sub>), 1735 (C=O) and 1645 cm<sup>-1</sup> (C=C); uv (95% EtOH), end absorption (ε 2400 at 210 nm) with

inflections at 235 nm ( $\epsilon$  1100) and 270 nm ( $\epsilon$  295); nmr ( $\text{CCl}_4$ ),  $\delta$  5.4-5.9 (2H, m, vinyl CH), 3.61 (3H, s,  $\text{OCH}_3$ ), 1.7-2.9 (8H, m, aliphatic CH), and 1.28 (3H, s,  $\text{CH}_3$ ); mass spectrum, m/e (rel. intensity) 192 ( $\text{M}^+$ , 10), 134 (23), 133 (100), 117 (34), 115 (19), 105 (70), and 91 (21).

Anal. Calcd for  $\text{C}_{12}\text{H}_{16}\text{O}_2$ : C, 74.97; H, 8.39.

Found: C, 75.00; H, 8.40.

#### Preparation of the Lactone 22

To a cold ( $-78^\circ$ ) suspension of 528 mg (2.54 mmol) of the acid 17 in 6 ml of  $\text{CH}_2\text{Cl}_2$  was added, dropwise and with stirring, 1.4 ml of a  $\text{CH}_2\text{Cl}_2$  solution containing 2.8 mmol of  $\text{BBr}_3$ . The resulting mixture, which rapidly changed to a clear yellow solution, was stirred at  $-78^\circ$  for about 1 min and then added to a cold ( $0^\circ$ ) mixture of 7 ml of saturated aqueous  $\text{NaHCO}_3$  and 7 ml of aqueous 0.8 M  $\text{KBr}_3$  ( $\text{KBr}$  and  $\text{Br}_2$ ). After the resulting two phase mixture had been stirred at  $0^\circ$  for 10 min, sufficient  $\text{Na}_2\text{S}_2\text{O}_3$  was added to consume the excess  $\text{Br}_2$  and the mixture was partitioned between  $\text{Et}_2\text{O}$  and aqueous  $\text{NaHCO}_3$ . After the ethereal solution had been dried and concentrated, the crude bromo lactone 21 remained as 675 mg of a colorless liquid which contained (tlc, silica gel coating with an  $\text{EtOAc}$ -hexane eluent, 1:4 v/v) the bromo lactone 21 ( $R_f$  0.38) and a minor unidentified impurity ( $R_f$  0.30). The crude bromo lactone 21 from a comparable experiment was partially purified by preparative tlc to obtain the bromo lactone 21 as a colorless semisolid; ir

(CHCl<sub>3</sub>), 1785 (γ lactone C=O) and 1725 cm<sup>-1</sup> (C=O); nmr CDCl<sub>3</sub>, δ 1.8-3.0 (10H, m, aliphatic CH) and 1.35 (3H, s, CH<sub>3</sub>). Samples of the crude bromo lactone 21 rapidly turned blue on standing.

A solution of the crude bromo lactone 21 (675 mg), 1.33 g (4.5 mmol) of n-Bu<sub>3</sub>SnH, and 5 mg of azobisisobutyryl-nitrile in 2 ml of benzene was heated to 55° with stirring under an N<sub>2</sub> atmosphere for 1 hr and then stirred for an additional 1 hr at 25°. The crude product contained (tlc) the lactone 22 (R<sub>f</sub> 0.19) and several components with higher R<sub>f</sub> values, but none of the starting bromo lactone was detected. The reaction mixture was concentrated and then chromatographed on silica gel with an EtOAc-hexane eluent (1:4 v/v). The crude lactone 22 obtained (364 mg, contaminated with tin compounds) was chromatographed a second time to separate 322 mg (65% based on the acid 17) of the lactone 22 as a colorless liquid that solidified on standing, mp 48-50°. Recrystallization from Et<sub>2</sub>O-pentane afforded 282 mg (57% based on acid 17) of the pure lactone 22 as colorless prisms: mp 51-52° (lit.<sup>3</sup> mp 45-47°); ir (CCl<sub>4</sub>), 1786 (γ lactone C=O) and 1725 cm<sup>-1</sup> (C=O); uv (95% EtOH), 299 nm (ε 53); nmr (CDCl<sub>3</sub>), δ 1.6-3.0 (11H, M, aliphatic CH) and 1.25 (3H, s, CH<sub>3</sub>); mass spectrum, m/e (rel. intensity), 194 (M<sup>+</sup>, 26), 151 (23), 111 (100), 108 (20), 95 (20), 55 (22), and 41 (20).

Anal. Calcd for C<sub>11</sub>H<sub>14</sub>O<sub>3</sub>: C, 68.02; H, 7.27.

Found: C, 68.09; H, 7.30.

The lactone 22 was identified with the previously described product<sup>3</sup> by comparison of ir and nmr spectra.



### References and Notes

1. M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzly, and H. J. E. Lowenthal, J. Org. Chem., **34**, 126 (1969); M. D. Bachi, J. W. Epstein, and H. J. E. Lowenthal, Tetrahedron Lett., 5333 (1966).
2. Chapter II, this thesis.
3. L. J. Dolby and C. N. Skold, J. Am. Chem. Soc., **96**, 3276 (1974). Spectra of keto lactone 22 were provided by Prof. Dolby.
4. All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated  $\text{MgSO}_4$  was employed as a drying agent. The ir spectra were determined with a Perkin Elmer, Model 257, infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary, Model 14, or a Perkin Elmer, Model 202, recording spectrophotometer. The proton nmr spectra were determined at 60 MHz with a Varian, Model A-60 or Model T-60-A, nmr spectrometer and the  $^{13}\text{C}$  nmr spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in  $\delta$  values (ppm) relative to a  $\text{Me}_4\text{Si}$  internal standard. The mass spectra were obtained with an Hitachi (Perkin Elmer), Model RMU-7, or a Varian, Model M-66, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.
5. J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, J. Chem. Soc., 112 (1959).
6. H. O. House, C. B. Hudson, and E. J. Racah, J. Org. Chem., **37**, 989 (1972).

## CHAPTER IV

## THE STRUCTURE OF A TRIMER OF ISOPHORONE

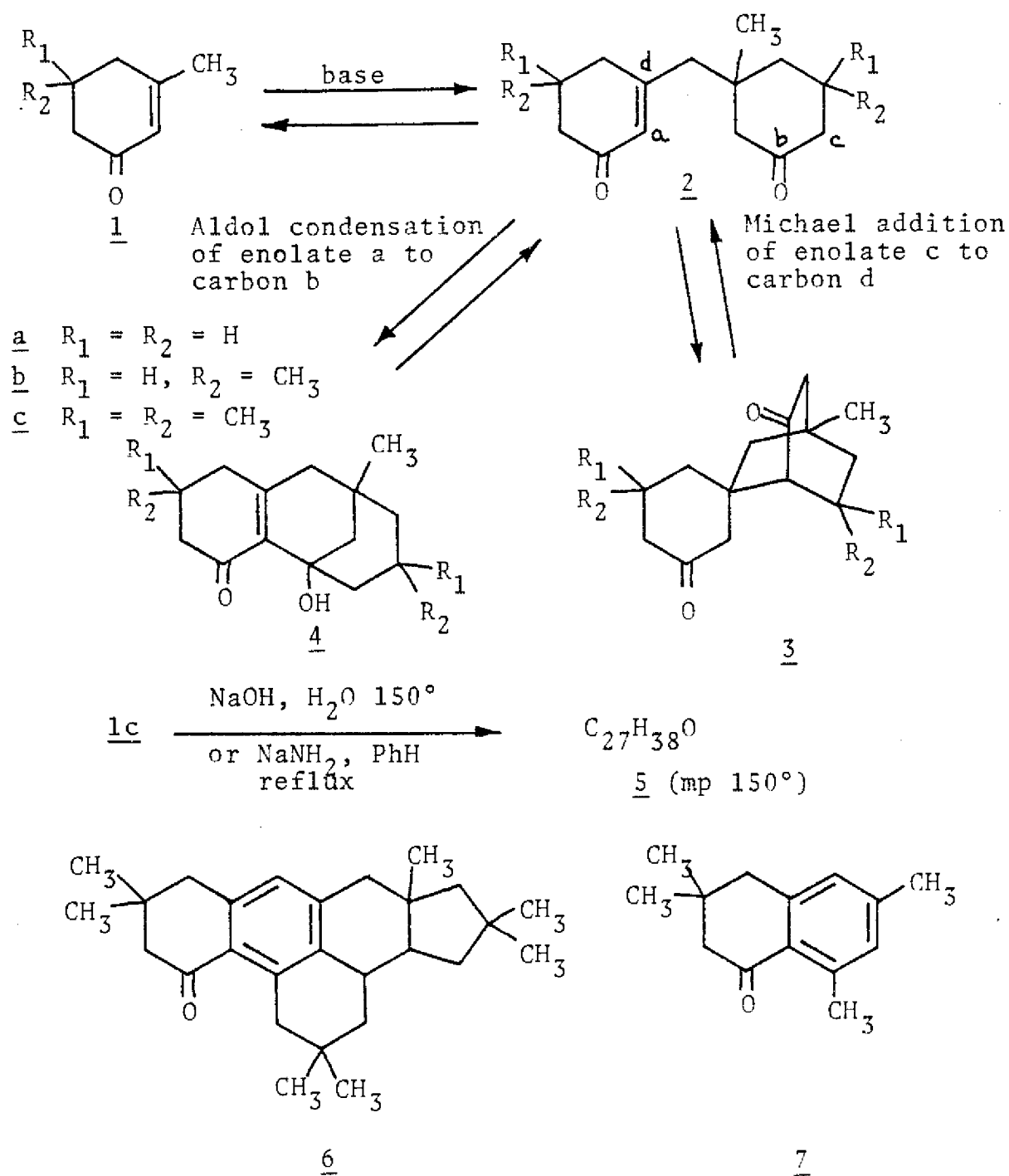
Discussion

The base catalyzed self condensation of 3-methylcyclohexenones (1) (scheme I) has been shown to give products of type 3<sup>2,3</sup> (kinetic control) or 4<sup>1,2,3,4</sup> (thermodynamic control) depending on the reaction conditions. These products can be visualized as arising from an initial Michael addition to give an intermediate 2, which can undergo either another intramolecular Michael addition to form the diketone 3 or an intramolecular aldol condensation to give the ketol 4.

When isophorone (1c) was heated to 150° with NaOH and H<sub>2</sub>O, in addition to recovered starting material and ketol 4c, there was also isolated a small amount of a yellow crystalline solid, mp 150-152° which had the composition C<sub>27</sub>H<sub>38</sub>O corresponding to three molecules of isophorone minus two molecules of H<sub>2</sub>O.<sup>3</sup> Apparently this same compound, mp 151-152°, was also isolated in about 25% yield along with about 5% of the diketone 3c when isophorone (1c) was refluxed with NaNH<sub>2</sub> in benzene.<sup>4</sup> This chapter describes the determination of the structure of this isophorone trimer.

The isophorone trimer (5) was prepared<sup>5</sup> in 14% yield using somewhat more vigorous conditions than had been

Scheme I



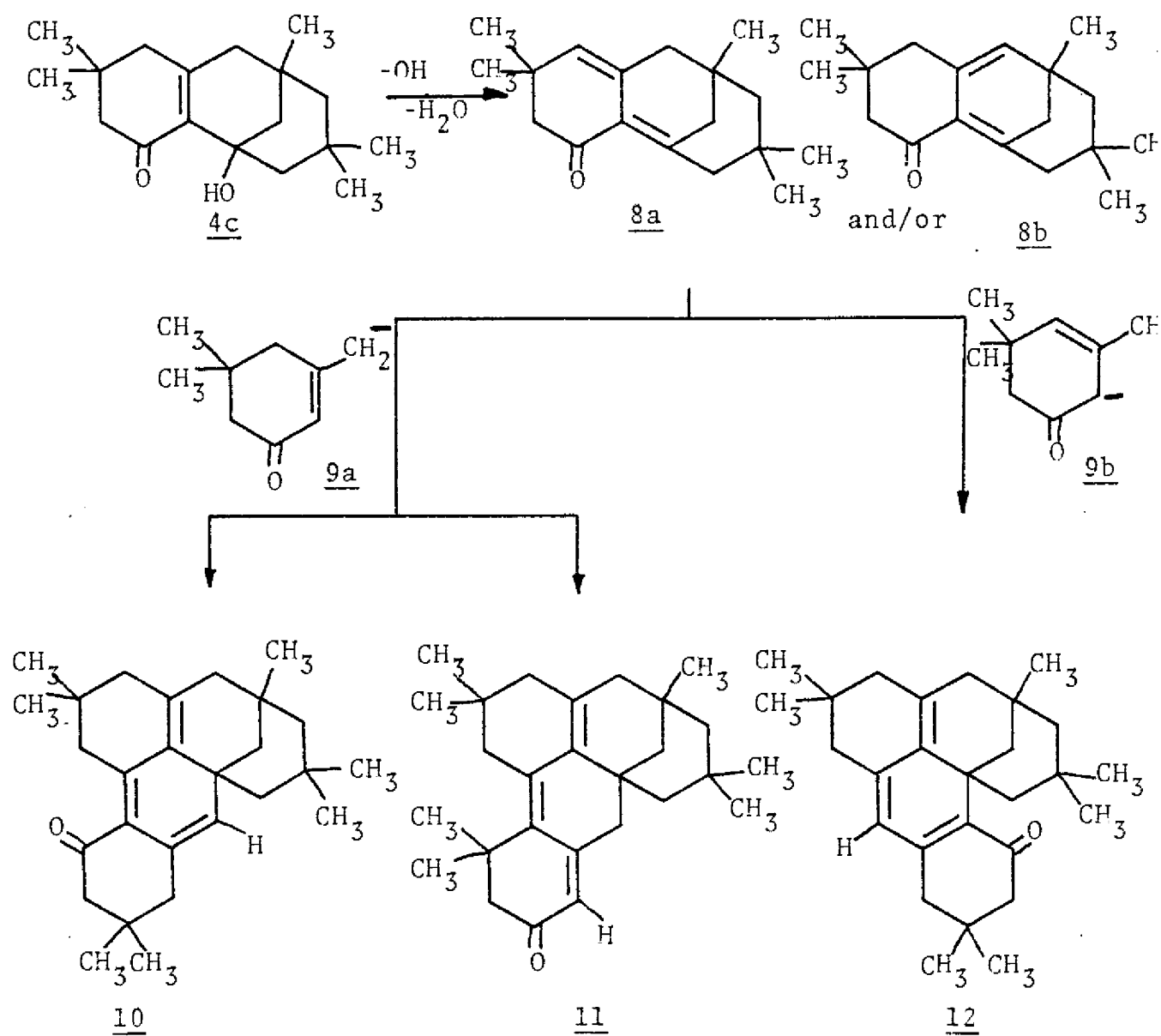
previously described<sup>3</sup> (see experimental section). The trimer 5 showed infrared bands at 1642 (C=O), 1628 (C=C), and 1618  $\text{cm}^{-1}$  (C=C) and ultraviolet maxima (95% EtOH) at 242 ( $\epsilon$  12000) and 390 nm ( $\epsilon$  8400). The  $^1\text{H}$  nmr spectrum had distinctive absorption at  $\delta$  5.42 (1H) and at 2.92, (1H, doublet,  $J = 12.5$  Hz), and the mass spectrum had a molecular ion peak at  $m/e$  378 with an intense fragment peak at  $m/e$  307. The natural abundance  $^{13}\text{C}$  nmr spectrum exhibited a low field signal at 197.0 ppm (C=O) with six additional lines in the region 120.2-147.0 ppm attributable to  $\text{sp}^2$  hybridized carbon atoms. One of these lines (120.2 ppm) was split into a doublet in the off resonance decoupled spectrum, indicating a C-H.

Cyrot, Thoai, and Wiemann have reported the structure of a compound with the same chemical composition as the trimer 5 as structure 6<sup>6</sup> (scheme I). This compound was obtained in the product when isophorone vapor was passed through a tube heated to 380° and packed with magnesium pellets, and the structure was determined from an x-ray crystallographic study of an iodo derivative. Since these authors did not report the melting point or any spectral data on their compound, a direct comparison with the trimer 5 was not possible; but it appeared unlikely that the trimer 5 did have structure 6. The absorption in the  $^1\text{H}$  nmr spectrum at  $\delta$  5.42 is not compatible with an aromatic hydrogen and seems more appropriate for a vinyl group, and the intense

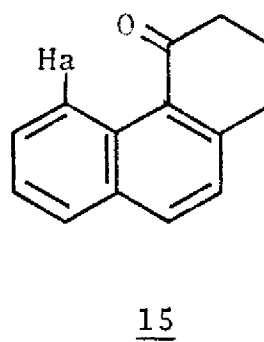
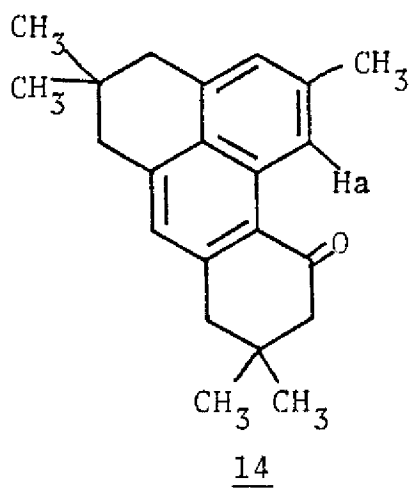
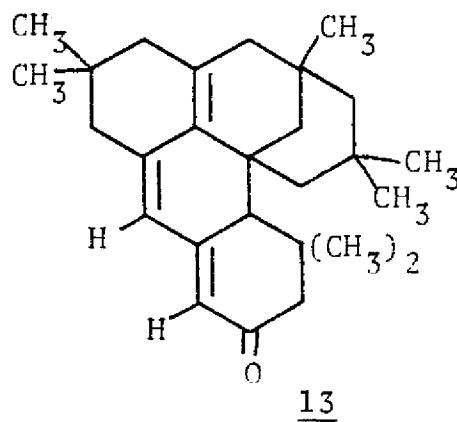
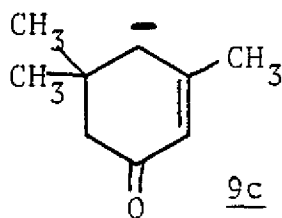
absorption at 390 nm in the ultraviolet spectrum did not seem likely for the benzyl ketone chromophore present in 6. The model tetralone 7 has aryl C-H absorption in the  $^1\text{H}$  nmr spectrum at  $\delta$  6.88 and ultraviolet maxima at 261 ( $\epsilon$  14,000) and 300 nm ( $\epsilon$  2000).

One mechanistic possibility led to structures which fit the chemical formula and which are in general agreement with the spectral data observed for trimer 5. The action of base on the ketol 4c (scheme II) followed by elimination of  $\text{H}_2\text{O}$  would give the bridgehead enone 8. Although such a compound would be severely strained, similar compounds have been shown to exist.<sup>7</sup> Subsequent Michael addition by one of the enolate anions 9a-9c derived from isophorone to the enone 8 followed by an intramolecular aldol condensation and loss of  $\text{H}_2\text{O}$  would then give one of the products 10-13. Structure 13 can be eliminated immediately on spectral grounds since it contains two vinyl hydrogens. Of the remaining three structures, the calculated longest wavelength maximum of 397 nm for structure 11 is consistent with the observed value of 390 nm. The calculated value for structure 12 is 417 nm; and for structure 10, no calculation can be made since it contains a cross conjugated system. The doublet at  $\delta$  2.92 in the  $^1\text{H}$  nmr spectrum, which appeared to be one half of an AX system, is in agreement with either structures 10 or 12. Both have one hydrogen of a methylene group in close proximity to the carbonyl oxygen. No similar

## Scheme II

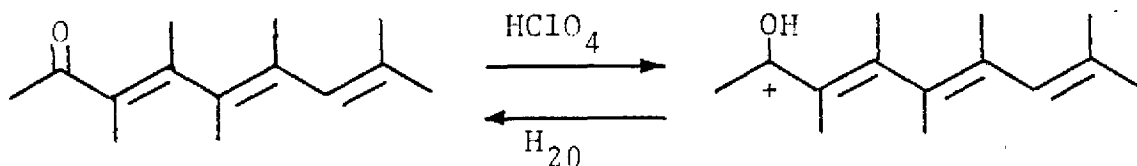


## Scheme II (cont.)



structural feature exists in 11.

Two other experimental results were in support of this general idea and allowed a reasonable choice to be made from the alternative structures. When trimer 5 was treated with 70%  $\text{HClO}_4$  in  $\text{CH}_2\text{Cl}_2$ , removal of the solvent left a dark red solid which could be reconverted to the trimer 5 upon treatment with aqueous acetone. The  $^{13}\text{C}$  nmr spectrum (see experimental section) of this red solid was similar to that of the trimer 5, but three of the six vinyl carbons were shifted by 20-30 ppm to lower field. The infrared spectrum lacked any strong absorption in the carbonyl region, but showed instead a series of weak bands at 1642, 1605, and  $1585\text{ cm}^{-1}$ ; and the ultraviolet maxima were shifted to higher wavelengths. These results are consistent with this material being a linearly conjugated trienone which has been protonated on oxygen and has the positive charge delocalized over alternate carbon atoms. This structural feature is present in 11 and 12 but not in 10.

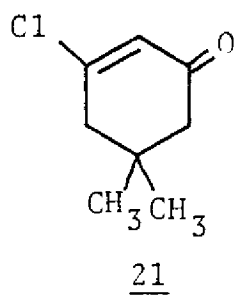
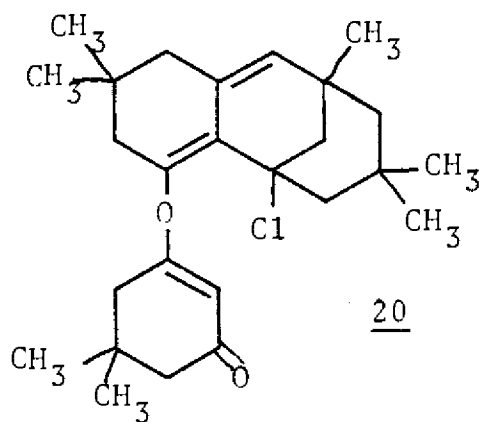
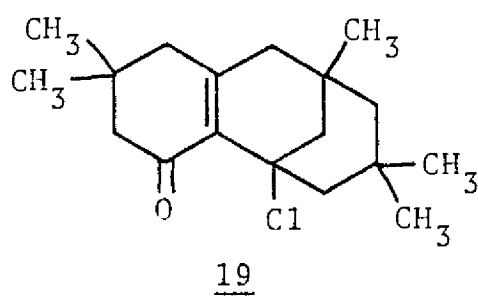
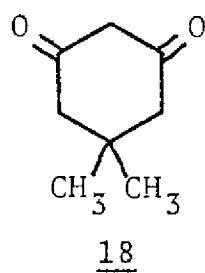
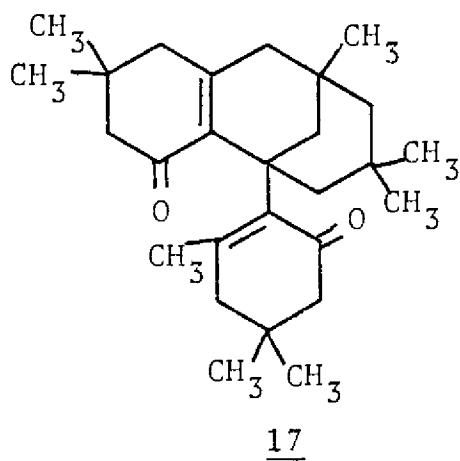
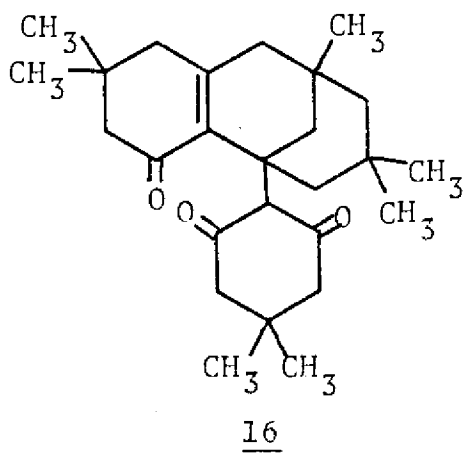




The second experiment resulted from the observation that the trimer 5 had a tendency to lose in the mass spectrometer fragments totaling 71 mass units to give a stable charged fragment of  $m/e$  307. To see if this decomposition could be duplicated by a thermal process, the trimer 5 was heated to boiling (300-320°) and the resulting products were chromatographed. A crystalline solid of molecular weight, 306, the combustion analysis and spectral data (see experimental section) of which were compatible with the naphthyl ketone structure 14 (scheme II), was isolated in 34% yield. In particular, one especially low field aromatic hydrogen at  $\delta$  9.18 in the  $^1\text{H}$  nmr spectrum was similar to that found for the naphthyl ketone 15.<sup>8</sup> This compound could arise from decomposition of a compound having structure 12; and although similar processes can be imagined for both structures 10 and 11, the analagous naphthyl ketones would not have an aromatic hydrogen similarly placed to the carbonyl or in any other way which would account for the nmr spectrum.

Since it appeared likely from the evidence described above that the isophorone trimer 5 had structure 12, it was decided to clarify this point with an unambiguous synthesis of the compound having this structure. A reasonable intermediate for the synthesis of trienone 12 appeared to be the triketone 16 (scheme III). Elaboration of one of the carbonyl groups in the  $\beta$ -dicarbonyl system to a methyl group would give diketone 17, which could then give trienone 12 by an

## Scheme III



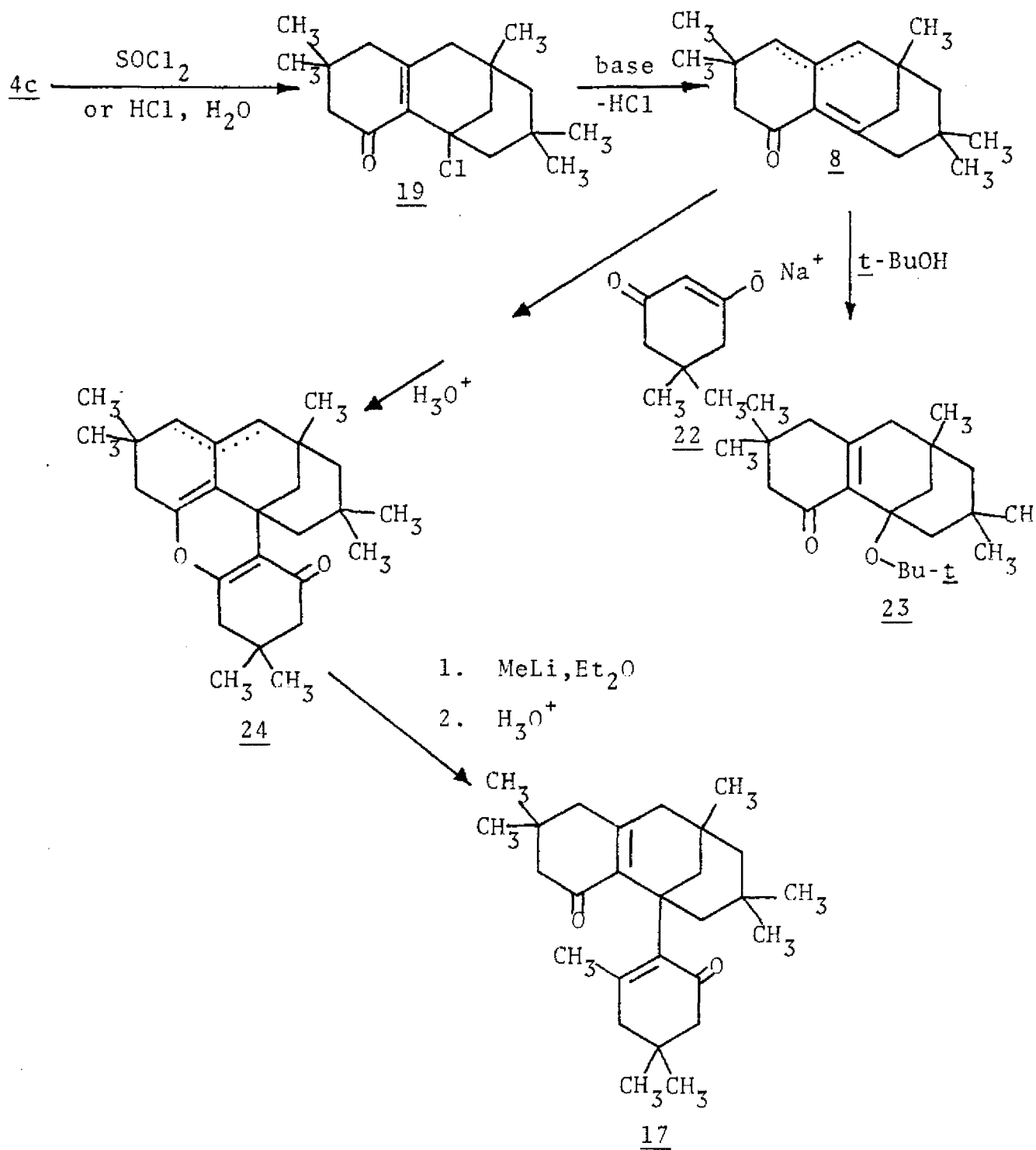
intra-molecular aldol condensation.

The first approach to triketone 16 that was tried was the alkylation of the  $\beta$ -diketone 18 by the bridgehead chloride 19 in the presence of  $\text{AgClO}_4$  according to the method of Boldt and coworkers.<sup>9</sup> At 25° a precipitate of  $\text{AgCl}$  formed immediately upon mixing the reactants, but the product appeared to be derived mainly from alkylation on oxygen. Higher temperatures gave complex mixtures. In order to prevent O-alkylation, an attempt was made to synthesize the enol ether 20 from the chloride 19 and the  $\beta$ -chloro enone 21. Depending on the reaction conditions, either the starting materials or complex mixtures were recovered.

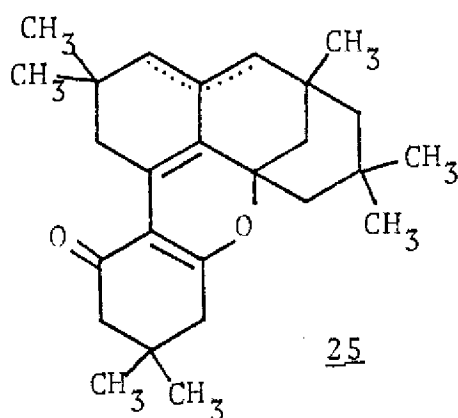
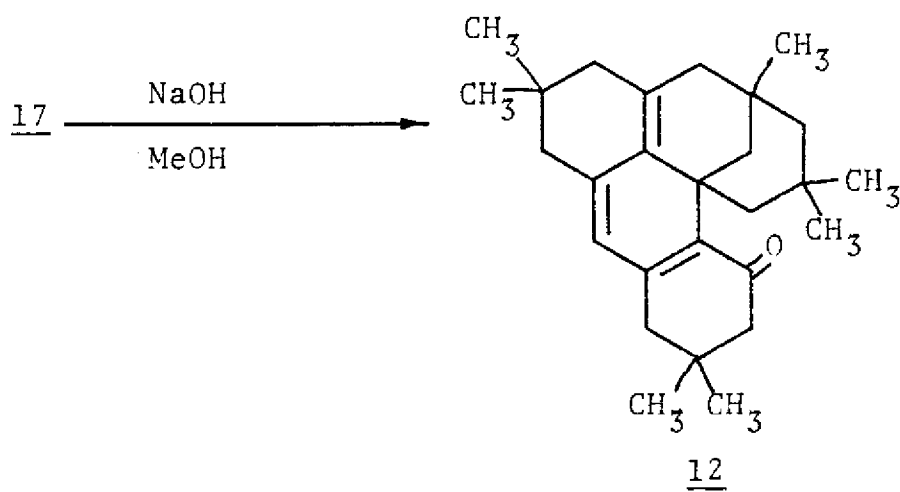
The second approach that was considered and which was eventually successful, was to use the bridgehead enone 8 (scheme II) as a reactive intermediate. The chloride 19 (scheme IV) was treated with *t*-BuOK in *t*-BuOH-THF at 25° to give the *t*-butoxy ketone 23 as the major product. Since, in the absence of base, the chloride 19 was stable in refluxing *t*-BuOH, and back side attack on chloride is precluded by the molecular structure, the only reasonable mechanism to give the *t*-butoxy ketone 23 is an elimination-addition mechanism involving the bridgehead enone 8. This experiment showed that the bridgehead enone 8 had at least transient existence.

The chloride 19 in the presence of NaH and the sodium salt of dimedone (22) gave, following an acid catalyzed

Scheme IV



## Scheme IV (cont.)



dehydration, the keto enol ether 24 in 53% yield. The structure follows from its spectral properties and method of preparation (see experimental section). A possible alternative structure 25 was rejected on the basis of the  $^{13}\text{C}$  nmr spectrum. Two lowfield  $\text{sp}^2$  carbon signals at 142.5 and 165.2 ppm can be attributed to the two  $\text{sp}^2$  carbons attached to oxygen in structure 24. Structure 25 has only one such carbon. In addition, the low field signal from the  $\text{sp}^3$  carbon attached to oxygen expected from compound 25 (e.g. 70.9 ppm in the spectrum of ketol 4c) is absent. The addition of  $\text{CH}_3\text{Li}$  to the carbonyl group of keto enol ether 24 followed by an acid catalyzed hydrolysis gave the diketone 17 in 57% yield. A base catalyzed intramolecular aldol cyclization of diketone 17 then gave the trienone 12 in 80% yield. Trienone 12 was found to be identical in all respects to the trimer 5, and the sequence of reactions used for its preparation provided strong evidence in favor of the mechanism proposed for its formation from the base catalyzed self condensation of isophorone.

The list of bond lengths and bond angles in Table 1, and the perspective view of the trienone 12 shown in Figure 1 are taken from the results of a single crystal x-ray study run in conjunction with the total synthesis described above.<sup>10</sup> The results of the two studies are completely compatible. The x-ray structure reveals that there is some distortion from planarity in the conjugated system extending

Table 1. Molecular Geometry of the Trienone 12

## (a) Bond Lengths

Atoms	Distance, Å (standard deviation)	Atoms	Distance, Å (standard deviation)
O-C1	1.213 (4)	C13-C14	1.495 (5)
C5-C6	1.353 (4)	C14-C15	1.518 (5)
C7-C8	1.329 (5)	C15-C16	1.514 (5)
C9-C14	1.334 (4)	C16-C17	1.523 (5)
C1-C6	1.481 (4)	C8-C17	1.508 (5)
C5-C7	1.452 (5)	C10-C20	1.557 (5)
C8-C9	1.450 (5)	C12-C18	1.534 (5)
C1-C2	1.506 (5)	C18-C19	1.537 (6)
C2-C3	1.524 (5)	C19-C20	1.544 (5)
C3-C4	1.516 (5)	C3-C21	1.520 (5)
C4-C5	1.511 (5)	C3-C22	1.520 (5)
C9-C10	1.526 (5)	C16-C23	1.530 (6)
C6-C10	1.543 (5)	C16-C24	1.517 (6)
C10-C11	1.534 (5)	C12-C25	1.520 (6)
C11-C12	1.529 (5)	C19-C26	1.527 (6)
C12-C13	1.524 (5)	C19-C27	1.529 (6)

## (b) Bond Angles

Atoms	Angle, ° (standard deviation)	Atoms	Angle, ° (standard deviation)
O-C1-C2	119.9 (4)	C9-C10-C20	109.9 (3)
O-C1-C6	123.1 (3)	C11-C10-C20	107.8 (3)
C2-C1-C6	117.0 (3)	C10-C11-C12	111.0 (3)
C1-C2-C3	112.5 (3)	C11-C12-C13	107.7 (3)
C2-C3-C4	106.1 (3)	C11-C12-C18	108.7 (3)
C2-C3-C21	110.1 (3)	C11-C12-C25	110.5 (3)
C2-C3-C22	110.5 (3)	C13-C12-C18	113.2 (3)

Table 1 (concluded)

## (b) Bond Angles (cont.)

Atoms	Angle, ° (standard deviation)	Atoms	Angle, ° (standard deviation)
C4-C3-C21	110.7 (3)	C13-C12-C25	109.1 (3)
C4-C3-C22	110.3 (3)	C18-C12-C25	107.7 (3)
C21-C3-C22	109.2 (4)	C12-C13-C14	116.3 (3)
C3-C4-C5	116.1 (3)	C13-C14-C9	122.6 (3)
C4-C5-C6	123.0 (3)	C13-C14-C15	115.1 (3)
C4-C5-C7	115.8 (3)	C9-C14-C15	122.2 (3)
C6-C5-C7	121.2 (3)	C14-C15-C16	116.7 (3)
C5-C6-C10	119.5 (3)	C15-C16-C17	107.3 (3)
C1-C6-C5	118.2 (3)	C15-C16-C23	110.3 (4)
C1-C6-C10	122.0 (3)	C15-C16-C24	109.3 (4)
C5-C7-C8	121.6 (3)	C17-C16-C23	110.0 (4)
C7-C8-C9	120.6 (3)	C17-C16-C24	110.6 (3)
C7-C8-C17	122.8 (3)	C23-C16-C24	109.3 (4)
C9-C8-C17	116.6 (3)	C16-C17-C8	112.5 (3)
C8-C9-C10	117.4 (3)	C12-C18-C19	119.5 (3)
C8-C9-C14	120.4 (3)	C18-C19-C20	110.8 (3)
C10-C9-C14	122.2 (3)	C18-C19-C26	108.8 (3)
C6-C10-C9	110.8 (3)	C18-C19-C27	111.6 (3)
C6-C10-C11	113.4 (3)	C20-C19-C26	107.9 (3)
C6-C10-C20	106.0 (3)	C20-C19-C27	111.7 (3)
C9-C10-C11	108.9 (3)	C26-C19-C27	105.7 (4)
		C19-C20-C10	116.3 (3)



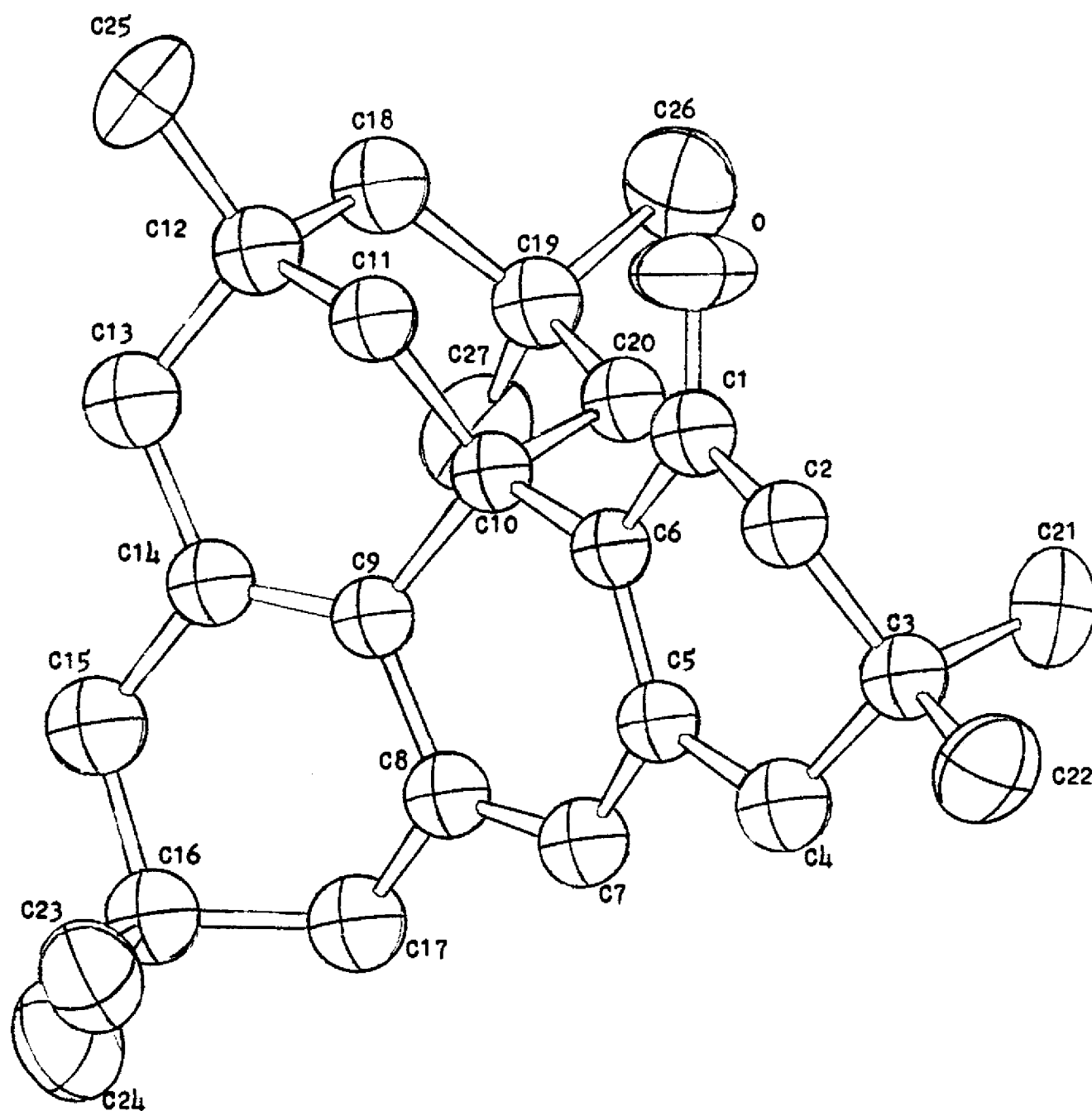


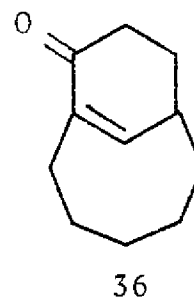
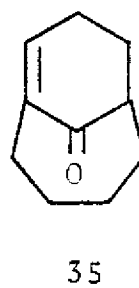
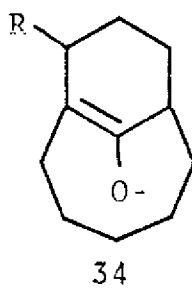
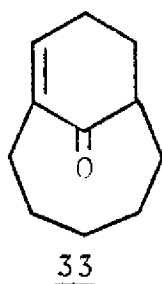
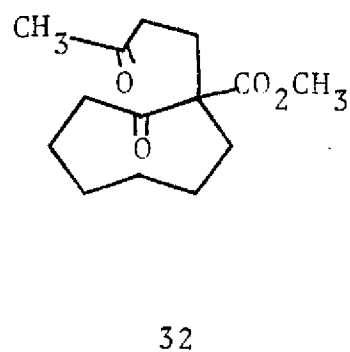
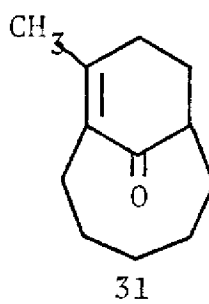
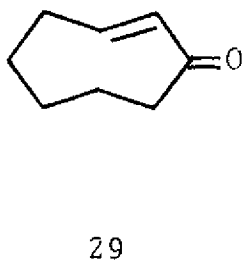
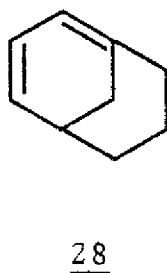
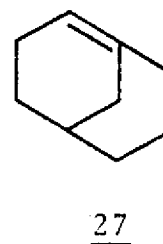
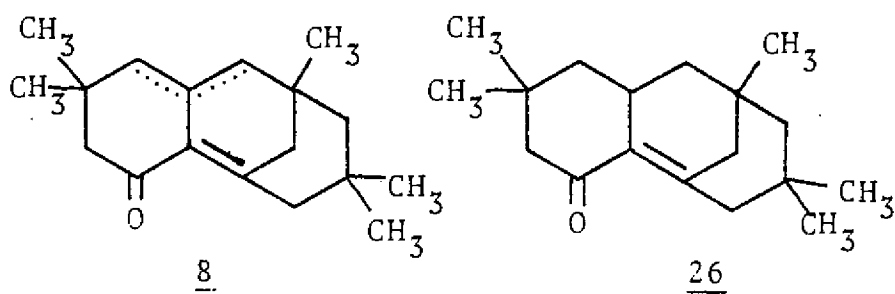
Figure 1. A Perspective View of the Molecular Structure of the Trienone 12

from the carbonyl group (C1) to C14. Dihedral angle calculations about the bonds C1-C6, C5-C7, and C8-C9 all show approximately  $15^\circ$  twists from planarity, which may account for the discrepancy observed in the ultraviolet maximum of 390 nm and the calculated value of 417 nm. Repulsion between the carbonyl O and a methylene hydrogen at C11 (H11-O distance of 2.32 Å compared to 2.5 Å required for the sum of the van der Waals radii) is apparently responsible for some of this distortion, and is consistent with the low field signal observed in the  $^1\text{H}$  nmr spectrum.

After it was determined that the strained intermediate dienone 8 (scheme V) did have at least transient existence, the question arose of whether or not such a species could be isolated and studied. The enone 26 would be more suitable for characterization since it lacks any of the complications due to the second double bond, and there is precedent with strained olefin systems that it would probably be more stable. Whereas the olefin 27 has been purified and characterized,<sup>7a,b</sup> the diene 28 could only be generated and trapped.<sup>11</sup>

Some work on various strained and bridgehead enone systems has appeared in the literature. Trans cyclooctenone (29) has been generated by photoinduced isomerization of the cis isomer.<sup>12</sup> However, it dimerizes on standing and could not be separated from some contaminating cis isomer. Trans cycloheptenone (30) has also been generated by photoinduced isomerization of the cis isomer.<sup>13,14</sup> It is considerably

## Scheme V

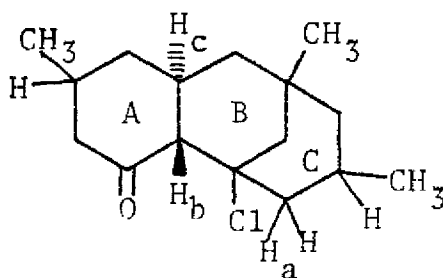


less stable than trans cyclooctenone. The enone 31, which has the bridgehead double bond trans in a ten membered ring, was prepared by Prelog and coworkers by intramolecular condensation of the diketo ester 32 with concentrated  $\text{H}_2\text{SO}_4$ .<sup>15</sup> This compound was prepared in a study to determine the limits of Bredt's rule, and at the time it was believed that it represented the minimum ring size which could accomodate a bridgehead double bond. The enone 33, which is similar to 31, has been prepared by basic elimination of the corresponding  $\beta$ -tosylate.<sup>16</sup> This enone is stable except for a tendency to isomerize to the  $\beta,\gamma$ -unsaturated isomer. One notable feature of enone 33 is its inability to undergo Michael additions.<sup>16b</sup> Addition of some nucleophile to 33 would give as an intermediate the enolate 34, which has a trans double bond in an eight membered ring. The lower homologue 35 which has a trans cyclononene ring, has been prepared by pyrolysis of the  $\beta$ -benzoate. This compound is stable and also does not undergo Michael additions.<sup>17</sup> The enone 36, which is isomeric to 33 but which has a trans cyclooctene ring, has been prepared by basic elimination of the corresponding mesylate.<sup>16b</sup> Although it could be obtained pure, it apparently was too unstable for chemical studies and decomposed on standing.

Attempts to reduce the double bond in ketol 4c with metal in ammonia gave a mixture of products from which no useful material could be obtained. Because of a report by

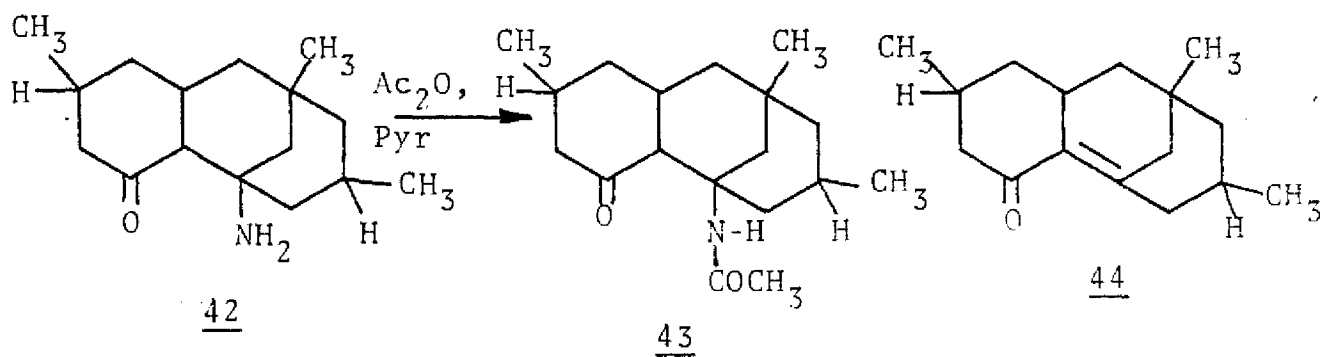
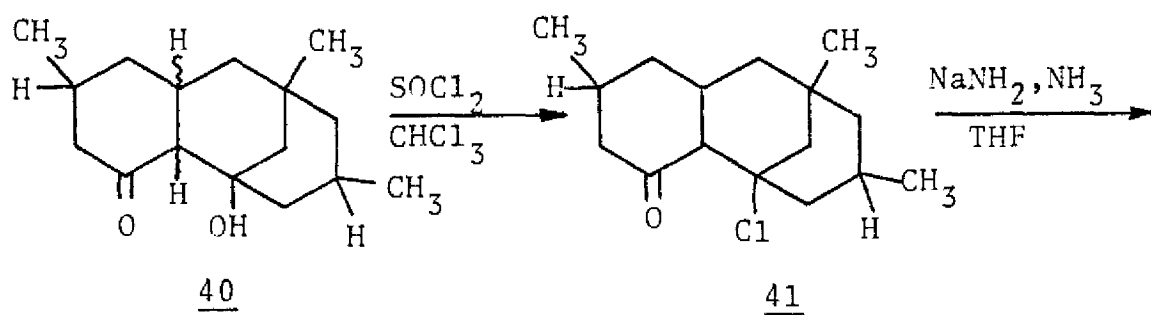
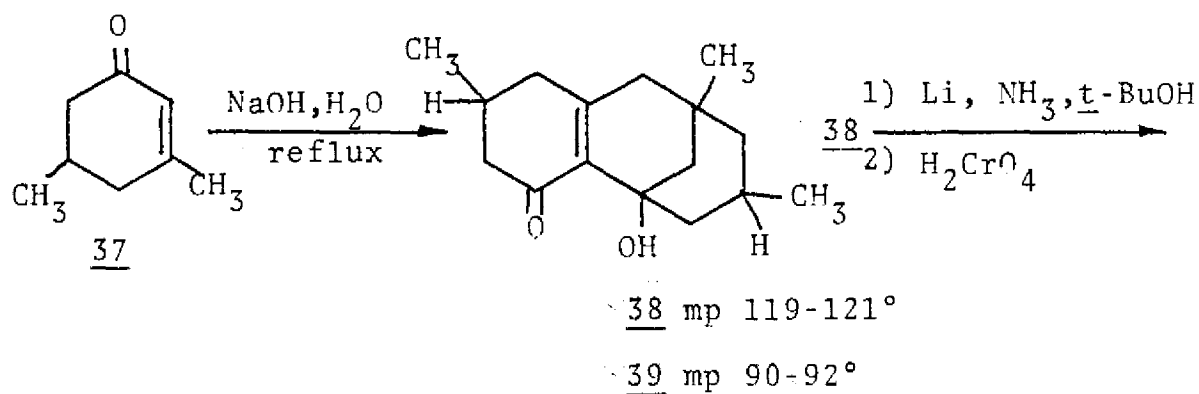
Ayer and Taylor, who claimed to have prepared the analogous ketol 40<sup>1</sup> (scheme VI), 3,5-dimethylcyclohexenone (37) was dimerized with aqueous NaOH to give the known<sup>1</sup> ketol 38 as well as an isomer, 39. The ketol 38 was reduced with Li in ammonia containing t-BuOH to give a mixture of products from which, after oxidation with Jone's reagent, one crystalline isomer of the dihydro ketol 40 could be isolated in 32% yield. This compound had a melting point in agreement with the literature.<sup>1</sup> The ketol 40 was converted to the chloro ketone 41 with SOCl<sub>2</sub> in CHCl<sub>3</sub>.

The <sup>1</sup>H nmr spectrum of chloroketone 41 showed a doublet of doublets ( $J = 4.3, 12.6$  Hz) centered at  $\delta$  3.33 which integrated for one hydrogen, and also a doublet ( $J = 12$  Hz) at  $\delta$  2.55 which also integrated for one hydrogen. A model of chloroketone 41 shows that one hydrogen marked a



is close to the carbonyl oxygen and within the deshielding zone when the C ring is in a chair conformation and the hydrogen marked b is  $\beta$ . The splitting pattern at  $\delta$  3.33

## Scheme VI



would then be reasonable for the hydrogen marked a (vicinal and geminal coupling). The coupling constant for the doublet at  $\delta$  2.55 is reasonable for  $H_b$  ( $\alpha$  to both a ketone and chloride) for a dihedral angle of either  $0^\circ$  or  $180^\circ$  between  $H_b$  and  $H_c$ . A model indicates that for an angle of  $0^\circ$  (cis ring junction) no stable conformation exists. In contrast, for a trans ring junction between rings A and B, the molecule is held rigid, with a dihedral angle of  $180^\circ$  between  $H_b$  and  $H_c$ .

A mixture of the chloro ketone 41, THF, and liquid  $NH_3$  was stirred with  $NaNH_2$ , and the amino ketone 42, after extraction from the crude product with dilute aqueous acid, was isolated in 50% yield. The amino ketone 42 was characterized as the keto amide 43, which has spectra consistent with the assigned structure.

Since back side displacement of chloride in 41 is impossible, the amino ketone 42 must arise from an elimination, addition mechanism involving the bridgehead enone 44 as an intermediate. No attempt was made to isolate the enone 44.

### Experimental Section<sup>18</sup>

#### Preparation of the Trienone 12

A mixture of 200 g (1.45 mol) of the enone 1c, 70 g of NaOH, and 30 ml of  $H_2O$  was heated to  $150^\circ$  with stirring for 20 hr and then cooled and partitioned between  $Et_2O$  and

H<sub>2</sub>O. The ethereal layer was washed with aqueous NaCl, dried, and concentrated to leave 198 g of crude product as a dark red liquid. The relatively volatile materials were removed from this mixture by distillation at 0.3 mm and temperatures up to 170°. When an EtOH solution of the residue from this distillation was cooled, the crude trienone 12 separated as a yellow solid, mp 138-144°. Recrystallization from EtOH gave 25.1g (14%) of the trienone 12 as yellow prisms, mp 147-148°. When this material was allowed to crystallize very slowly from EtOH, the trienone 12, mp 149-150°, separated as large yellow prisms (lit.<sup>3</sup> mp 150-152°); ir (CHCl<sub>3</sub>), 1642 (conjugated C=O), 1628, and 1618 cm<sup>-1</sup> (C=C); uv max (95% EtOH), 242 nm ( $\epsilon$  12,000) and 390 nm ( $\epsilon$  8400); <sup>1</sup>H nmr (CDCl<sub>3</sub>),  $\delta$  5.42 (1H, broad, vinyl CH), 2.92 (1H, d, J = 12.5 Hz, aliphatic CH), and 0.8-2.4 (36H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 378 (M<sup>+</sup>, 24), 363 (11), 308 (25), and 307 (100).

Anal. Calcd for C<sub>27</sub>H<sub>38</sub>O: C, 85.66; H, 10.12.

Found: C, 85.70; H, 10.13.

The EtOH mother liquors remaining after the above crystallization of the trienone 12 were concentrated to leave a brown viscous liquid containing (tlc, silica gel coating with an EtOAc-hexane eluent, 1:4 v/v) two or more rapidly eluted components with R<sub>f</sub> values of 0.59 (corresponds to the trienone 12) and 0.62 as well as several more polar components with smaller R<sub>f</sub> values. A portion of this crude mixture was



subjected to a preparative tlc separation to obtain a sample of the materials with  $R_f$  values of 0.59 and 0.62. GLPC analysis (silicone DC-710 on Chromosorb P) of the sample indicated the presence of comparable amounts of four components with the following retention times: 26.6 min; 31.0 min (corresponds to the trienone 12); 38.0 min; and 48.4 min. Thus, this base-catalyzed condensation of isophorone (4c) produces components other than the trienone 12 but with similar properties. These by-products may include one or more of the structural isomers 10, 11, and 13.

The natural abundance  $^{13}\text{C}$  nmr spectrum of the trienone 12 ( $\text{CDCl}_3$  solution) exhibited the peaks listed in Table 2. The results of off-resonance decoupling measurements (s, d, t, etc.) are indicated in parentheses beside each peak. In cases where close spacing of two peaks made the splitting pattern ambiguous, the multiplicity is designated with a question mark.

When a solution of 2.25g (5.95 mmol) of the trienone 12 in 10 ml of  $\text{CH}_2\text{Cl}_2$  was treated with 5 ml of aqueous 70%  $\text{HClO}_4$ , the organic layer immediately became deep red in color. After the mixture had been stirred at  $25^\circ$  for 30 min, the organic layer was separated, dried, and concentrated to leave 2.83g of the crude perchlorate salt of the trienone 12 as a red solid; ir ( $\text{CHCl}_3$ ), a series of weak bands in the  $6\mu$  region at 1642, 1605, and  $1585\text{ cm}^{-1}$  ( $\text{C}=\text{C}$ ); uv max ( $\text{CH}_2\text{Cl}_2$ ), 272 nm ( $\epsilon$  ca. 11,000), 329 nm ( $\epsilon$  ca. 2900), and 511 nm

( $\epsilon$  ca. 15,000);  $^1\text{H}$  nmr ( $\text{CDCl}_3$ ),  $\delta$  6.09 (1H, broad, vinyl CH), and 0.8-3.0 (37H, m, aliphatic CH). The natural abundance  $^{13}\text{C}$  nmr data obtained for a  $\text{CDCl}_3$  solution of this crude salt is summarized in Table 2; in some cases, designated (?), we were unable to discern the splitting patterns obtained with off-resonance decoupling. When a solution of 104 mg of this crude salt in 5 ml of acetone was treated with  $\text{H}_2\text{O}$ , the red color was discharged to leave a yellow solution. After this solution had been partitioned between  $\text{H}_2\text{O}$  and  $\text{CH}_2\text{Cl}_2$ , the organic layer was dried and concentrated to leave 83 mg of the crude trienone 12, mp 143.5-144.5°, that was identified with the starting trienone 12 by comparison of ir and uv spectra. Recrystallization from EtOH raised the melting point of the recovered trienone 12 to 148-149°; a mixture melting point determination of the starting and recovered trienone samples was not depressed.

#### Properties of the Tetralone 7<sup>19</sup>

The tetralone 7 was obtained as colorless prisms, mp 56-57° (lit. mp 56.5-57°, <sup>19b</sup> 54-55°<sup>19c</sup>); ir ( $\text{CCl}_4$ ), 1670  $\text{cm}^{-1}$  (conjugated C=O); uv max (95% EtOH), 261 nm ( $\epsilon$  14,000), and 300 nm ( $\epsilon$  2000); nmr ( $\text{CDCl}_3$ ),  $\delta$  6.88 (2H, broad s, aryl CH), 2.76 (2H, s,  $\text{CH}_2$ ), 2.60 (3H, s, aryl  $\text{CH}_3$ ), 2.41 (2H, s,  $\text{CH}_2$ ) 2.28 (3H, s, aryl  $\text{CH}_3$ ), and 1.00 (6H, s,  $\text{CH}_3$ ); mass spectrum, m/e (rel. intensity), 202 ( $\text{M}^+$ , 34), 146 (100), and 118 (9).

Table 2. Natural Abundance  $^{13}\text{C}$  NMR Spectra in  $\text{CDCl}_3$   
Solution of the Trienone 12 and Its  
Perchlorate Salt

Signal in order of increasing field	Signal for trienone <u>12</u> ppm (multiplicity in off-resonance decoupling) <sup>a</sup>	Signal for the salt, ppm (multiplicity in off-resonance decoupling) <sup>a</sup>
1	196.0 (s)	193.4 (s)
2	147.0 (s)	178.3 (s)
3	141.1 (s)	163.3 (s)
4	135.8 (s)	153.8 (s)
5	132.4 (s)	132.0 (s)
6	131.4 (s)	127.7 (s)
7	120.2 (d)	124.5 (d)
8	53.4 (t)	51.8 (t)
9	52.4 (t)	46.5 <sup>b</sup> (t,?)
10	45.8 (t)	46.4 <sup>b</sup> (t,?)
11	44.8 <sup>b</sup> (t,?)	46.4 <sup>b</sup> (t,?)
12	44.7 <sup>b</sup> (t,?)	46.3 <sup>b</sup> (t,?)
13	43.9 (t,?)	45.0 (t)
14	43.1 (t)	44.0 (t)
15	39.8 <sup>b</sup> (s)	40.3 <sup>b</sup> (s)
16	39.7 <sup>b</sup> (t)	40.3 <sup>b</sup> (?)
17	37.5 (q,?)	40.2 <sup>b</sup> (?)
18	33.2 (q)	37.3 (q)
19	32.6 (s)	32.8 <sup>b</sup> (s)
20	31.1 (q,?)	32.7 <sup>b</sup> (?)

Table 2 (concluded)

Signal in order of increasing field	Signal for trienone 12 ppm (multiplicity in off-resonance decoupling) <sup>a</sup>	Signal for the salt, ppm (multiplicity in off-resonance decoupling) <sup>a</sup>
21	30.3 <sup>b</sup> (s, ?)	32.1 (?)
22	30.3 <sup>b</sup> (s, ?)	30.4 <sup>b</sup> (?)
23	29.9 (s)	30.3 <sup>b</sup> (?)
24	29.2 <sup>b</sup> (q, ?)	29.9 (?)
25	28.9 <sup>b</sup> (q, ?)	29.5 (?)
26	26.6 (q)	26.9 (q)
27	25.4 (q)	25.2 (q)

<sup>a</sup>Where the multiplicity designation is accompanied by a question mark, the close spacing of two or more lines made the splitting pattern ambiguous.

<sup>b</sup>Only partial resolution of these closely spaced peaks was attained.

### Pyrolysis of the Trienone 12

A 2.00 g (5.29 mmol) sample of the trienone 12 was heated to boiling (ca. 320-330°) under an N<sub>2</sub> atmosphere during 30 min and then maintained at this temperature for 50 min. A solution of the product, a viscous brown liquid, in CH<sub>2</sub>Cl<sub>2</sub> was filtered through a bed of silica gel and then chromatographed on silica gel with a PhH-hexane eluent (3:1 v/v). After removal of the early fractions containing 1.13 g of viscous yellow liquid, subsequent fractions contained an oily solid that was triturated with pentane to leave 564 mg (34%) of the ketone 14 as a pale green solid, mp 141-143°. Recrystallization from EtOH afforded 475 mg of the pure ketone 14 as pale yellow-green needles, mp 143-144°, and an additional recrystallization raised the melting point to 143.5-145°; ir (CHCl<sub>3</sub>), 1660 cm<sup>-1</sup> (conjugated C=O); uv max (95% EtOH), 218 nm (ε 31,000), 258 nm (ε 22,000), and 343 nm (ε 8000); <sup>20</sup> <sup>1</sup>H nmr (CDCl<sub>3</sub>), δ 9.18 (1H, broad s, aryl CH), 7.07 (1H, broad s, aryl CH), 6.93 (1H, broad s, aryl CH), 2.83 (2H, s, benzylic CH<sub>2</sub>), 2.93 (4H, s, benzylic CH<sub>2</sub>), 2.57 (2H, s, benzylic CH<sub>2</sub>), 2.49 (3H, s, aryl-CH<sub>3</sub>), 1.09 (6H, s, CH<sub>3</sub>), and 0.99 (6H, s, CH<sub>3</sub>); mass spectrum, m/e (rel. intensity), 306 (M<sup>+</sup>, 100), 250 (53), 222 (10), 207 (13), and 192 (10).

Anal. Calcd for C<sub>22</sub>H<sub>26</sub>O: C, 86.23; H, 8.55.

Found: C, 86.04; H, 8.59.

The natural abundance <sup>13</sup>C nmr spectrum of a CDCl<sub>3</sub>

solution of the ketone 14 exhibited the peaks listed in Table 3.

#### Preparation of the Hydroxy Ketone 4c

Following a previous procedure,<sup>3</sup> a mixture of 117g (0.849 mol) of isophorone (1c), 20g of NaOH, and 10 ml of H<sub>2</sub>O was heated to 100-125° with stirring for 2 hr. After the reaction mixture had been partitioned between CHCl<sub>3</sub> and aqueous 3 M HCl, the organic layer was washed with aqueous NaCl, dried, and concentrated. The residual liquid was fractionally distilled to separate 14.3g of pale yellow liquid, bp 100° (15 min), and 86.63g of a viscous yellow liquid fraction, bp 110-133° (0.3 mm), that solidified on standing. Repeated recrystallization from hexane of the material from the latter fraction separated 51.8g (44%) of the pure ketol 4c as colorless prisms, mp 83-84° (lit. mp 84-85°,<sup>4</sup> 86-88°<sup>3</sup>); ir (CCl<sub>4</sub>), 3470 (OH), 1656 (shoulder), 1650 (conjugated C=O), and 1632 cm<sup>-1</sup> (C=C); uv max (95% EtOH), 250 nm ( $\epsilon$  8300); <sup>1</sup>H nmr (CCl<sub>4</sub>),  $\delta$  4.76 (1H, broad, OH), 1.1-2.2 (12H, m, CH<sub>2</sub>), 1.03 (6H, s, CH<sub>3</sub>), 0.98 (3H, s, CH<sub>3</sub>), 0.92 (3H, s, CH<sub>3</sub>), and 0.72 (3H, s, CH<sub>3</sub>); mass spectrum, m/e (rel. intensity), 276 (M<sup>+</sup>, 2), 261 (6), 206 (16), 205 (100), 163 (22), and 121 (19). The natural abundance <sup>13</sup>C nmr spectrum of the ketol 4c in CDCl<sub>3</sub> solution is summarized in Table 4.

#### Preparation of the Chloro Ketone 19

A solution of 9.78g (35.4 mmol) of the ketol 4c in 50

Table 3. Natural Abundance  $^{13}\text{C}$  NMR Spectrum of Ketone 14  
in  $\text{CDCl}_3$  Solutions

Signals in order of increasing field	$^{13}\text{C}$ nmr signal, ppm (multiplicity in off-resonance decoupling measurement)
1	199.1 (s)
2	143.9 (s)
3	141.7 (s)
4	137.7 (s)
5	134.2 (s)
6	131.0 (s)
7	126.5 (d)
8	126.4 (s)
9	124.9 (d)
10	123.5 (s)
11	123.2 (d)
12	54.5 (t)
13 and 14	45.2 (t)
15	44.7 (t)
16	33.3 (s)
17	30.5 (s)
18,19,20, and 21	27.8 (q)
22	22.1 (q)

Table 4. The Natural Abundance  $^{13}\text{C}$  NMR Spectrum of Ketol 4c in  $\text{CDCl}_3$  Solution

Signals in order of increasing field	$^{13}\text{C}$ nmr signal, ppm (multiplicity in off-resonance decoupling measurement)
1	194.4 (s)
2	156.3 (s)
3	134.7 (s)
4	70.9 (s)
5	51.9 (t)
6	51.5 (t)
7	50.1 (t)
8	46.4 (t)
9	45.5 (t)
10	44.4 (t)
11	36.9 (q)
12	32.5 (q)
13	32.2 (s)
14	32.0 (s)
15	31.2 (s)
16	29.5 (q)
17	28.1 (q)
18	26.6 (q)



ml of  $\text{CHCl}_3$  (EtOH free) was treated with 4.9g (41 mmol) of  $\text{SOCl}_2$  and the resulting solution was stirred at  $25^\circ$  for 16 hr. After the resulting solution had been washed successively with  $\text{H}_2\text{O}$  and with aqueous  $\text{NaHCO}_3$  it was dried and concentrated to leave 10.6g of the crude chloro ketone 19 as an orange solid. Recrystallization from MeOH afforded 8.02g of pure chloro ketone 19 as pale orange prisms, mp  $137\text{-}138.5^\circ$  (lit.<sup>3</sup> mp  $135\text{-}136^\circ$ ), as well as 0.97g of less pure product, mp  $136\text{-}138^\circ$  (total yield 8.99g or 86%); ir ( $\text{CCl}_4$ ), 1688, 1678 ( $\text{C=O}$ ), and  $1627\text{ cm}^{-1}$  ( $\text{C=C}$ ); uv max (95% EtOH), 244 nm ( $\epsilon$  8000); nmr ( $\text{CCl}_4$ ),  $\delta$  1.1-2.8 (12H, m,  $\text{CH}_2$ ), 1.08 (3H, s,  $\text{CH}_3$ ), 1.00 (6H, s,  $\text{CH}_3$ ), 0.93 (3H, s,  $\text{CH}_3$ ), and 0.73 (3H, s,  $\text{CH}_3$ ); mass spectrum, m/e (rel. intensity), 296 ( $\text{M}^+$ , 2), 294 ( $\text{M}^+$ , 5), 258 (40), 243 (33), 203 (25), 202 (40), 201 (100), 187 (30), 119 (24), 55 (25), and 41 (38).

#### Preparation of the Chloro Ketone 21

Following a previously described procedure,<sup>21</sup> a suspension of 20.0 g (0.14 mol) of dimedone (18) in 40 ml of  $\text{CHCl}_3$  (EtOH free) was treated with 6.7 g (0.049 mol) of  $\text{PCl}_3$  and the resulting mixture was refluxed for 2.2 hr. After the reaction mixture had been concentrated under reduced pressure, the residue was partitioned between  $\text{Et}_2\text{O}$  and aqueous 10% NaOH and the ethereal phase was dried and concentrated. Fractional distillation of the crude organic product afforded 13.6 g (61%) of the chloro ketone 21 as a colorless liquid, bp  $99\text{-}100^\circ$  (16 mm),  $n_D^{25}$  1.4943 [lit. bp

72° (5 mm),<sup>22</sup> 105° (20 mm),<sup>23</sup>]; ir (CCl<sub>4</sub>), 1700 (shoulder), 1682, 1670 (shoulder, conjugated C=O), and 1615 cm<sup>-1</sup> (C=C); uv max (hexane), 233 nm ( $\epsilon$  13,000); nmr (CCl<sub>4</sub>),  $\delta$  6.13 (1H, t, J = 1.5 Hz, vinyl CH), 2.55 (2H, d, J = 1.5 Hz, allylic CH<sub>2</sub>), 2.18 (2H, s, CH<sub>2</sub>CO), and 1.10 (6H, s, CH<sub>3</sub>); mass spectrum, m/e (rel. intensity) 160 (M<sup>+</sup>, 9), 158 (M<sup>+</sup>, 25), 143 (6), 104 (33), 102 (100), 67 (28), and 39 (16).

#### Preparation of the t-Butoxy Ketone 23

To a boiling solution of 700 mg (2.38 mmol) of the chloro ketone 19 in 5 ml of t-BuOH was added, dropwise and with stirring during 5 min, 5 ml of a t-BuOH solution containing 2.69 mmol of t-BuOK. During this addition the solution turned deep red and a fine precipitate (presumably KCl) separated. After the reaction mixture had been refluxed for 30 min, it was neutralized by addition of 0.5 g (9 mmol) of solid NH<sub>4</sub>Cl and then diluted with Et<sub>2</sub>O, filtered, and concentrated. The residue was partitioned between pentane and H<sub>2</sub>O and the pentane solution was dried and concentrated to leave 687 mg of the crude product as a light orange solid, mp 110-118°. Chromatography on silica gel with an EtOAc-hexane eluent (1:9 v/v) separated 484 mg (61%) of the t-butoxy ketone 23, mp 126-129°. Recrystallization from an EtOH-H<sub>2</sub>O mixture afforded the pure t-butoxy ketone 23 as colorless needles, mp 131-132°; ir (CCl<sub>4</sub>), 1671, 1680 (conjugated C=O), 1630 and 1620 cm<sup>-1</sup> (weak, conjugated C=C); uv max (95% EtOH), 248 nm ( $\epsilon$  6500); nmr (CCl<sub>4</sub>),  $\delta$  1.3-2.5 (10H, m, aliphatic CH)

and 0.6-1.3 [26H, m, aliphatic CH including singlets at 1.17 (t-BuO), 1.05 (CH<sub>3</sub>), 0.98 (two CH<sub>3</sub>), 0.81 (CH<sub>3</sub>), and 0.74 (CH<sub>3</sub>); mass spectrum, m/e (rel. intensity), 302 (2), 258 (12), 243((10), 231 (10), 205 (30), 187 (15), 146 (14), 56 (39), 55 (28), 41 (100), and 39 (35).

Anal. Calcd for C<sub>22</sub>H<sub>36</sub>O<sub>2</sub>: C, 79.46; H, 10.92.

Found: C, 79.44; H, 10.93.

In a similar experiment, a solution of 800 mg (2.72 mmol) of the chloro ketone 19 in 5 ml of THF was added to 5 ml of a t-BuOH solution containing 3.67 mmol of t-BuOK. The mixture, which turned red and deposited a white precipitate (KCl), was stirred at 25° for 12 hr and then subjected to the previously described isolation and purification procedures. The yield of the t-butyl ether 23, mp 130-132°, was 581 mg (64%).

As a control experiment, a solution of 150 mg (0.51 mmol) of the chloro ketone 19 in 2 ml of t-BuOH was refluxed for 25 min and then concentrated under reduced pressure. The recovered chloro ketone 19 (150 mg, mp 137-138.5°) was identified with an authentic sample by comparison of ir spectra.

#### Preparation of the Keto Enol Ether 24

To a cold (0°) suspension of 21 mmol of NaH (from 956 mg of a 52% dispersion that was washed with pentane) in 5 ml of DMF was added, dropwise and with stirring, a solution of 1.39 g (9.94 mmol) of dimedone (18) in 5 ml of DMF. After

the addition was complete, during which time the temperature of the mixture rose to 5°, a solution of 1.40 g (4.76 mmol) of the chloro ketone 19 in 10 ml of DME was added dropwise and with stirring during 5 min. During this addition the mixture became red-brown in color and gas was evolved. The resulting mixture was stirred at 5° for 20 min and at 25° for 80 min. The resulting mixture was diluted with H<sub>2</sub>O and then partitioned between Et<sub>2</sub>O and aqueous 1 M HCl. After the ethereal solution had been washed with H<sub>2</sub>O, dried, and concentrated, the residual crude product (2.00 g of viscous yellow liquid) was dissolved in 20 ml of THF containing 0.2 ml of aqueous 70% HClO<sub>4</sub> and stirred at 25° for 1.5 hr. The resulting mixture was partitioned between Et<sub>2</sub>O and aqueous 5% NaOH and the ethereal layer was washed with water, dried, and concentrated. Recrystallization of the residual crude product (1.39 g of tan solid, mp 140-150°) from EtOH separated 956 mg (53%) of the ketone 24 as colorless prisms, mp 160-162°. An additional recrystallization gave the pure ketone 24, mp 161-162°; ir (CCl<sub>4</sub>), 1680 (enol ether C=C), 1661 (conjugated C=O), and 1610 cm<sup>-1</sup> (conjugated C=C); uv max (95% EtOH), 240 nm ( $\epsilon$  18,000) and 318 nm ( $\epsilon$  2300); nmr (CCl<sub>4</sub>),  $\delta$  5.15 (1H, s, broad vinyl CH), 2.71 (1H, d, J = 12 Hz, aliphatic CH), 1.2-2.5 (13H, m, aliphatic CH), and 0.7-1.2 (21H, m, CH<sub>3</sub>); mass spectrum, m/e (rel. intensity), 380 (M<sup>+</sup>, 9), 365 (14), 310 (14), 309 (100), 83 (10), 55 (10), 43 (9), and 41 (9).

Anal. Calcd for  $C_{26}H_{36}O_2$ : C, 82.06; H, 9.54.

Found: C, 81.98; H, 9.55.

The natural abundance  $^{13}C$  nmr spectrum of the ketone 24 ( $CDCl_3$  solution) exhibited the peaks listed in Table 5.

Preparation of the Diketone 17 and the Trienone 12

To 3.1 ml of a cold ( $0^\circ$ ) ethereal solution containing 2.26 mmol of MeLi was added a solution of 588 mg (1.55 mmol) of the keto enol ether 24 in 7 ml of  $Et_2O$ . After the resulting mixture had been stirred at  $25^\circ$  for 20 min, it was partitioned between  $Et_2O$  and  $H_2O$ . The ethereal solution was dried and concentrated to leave a colorless viscous liquid that was dissolved in 10 ml of cold ( $0^\circ$ ) THF. This cold solution was treated with 2 ml of aqueous 12 M HCl in 5 ml of THF and the resulting solution was stirred at  $25^\circ$  for 1.5 hr. The resulting yellow solution was partitioned between aqueous NaCl and  $Et_2O$ . The ethereal layer was washed successively with aqueous  $NaHCO_3$  and with aqueous NaCl, dried, and concentrated to leave 614 mg of viscous yellow liquid containing (tlc, silica gel with an EtOAc-hexane eluent, 1:9 v/v) the diketone 17 ( $R_f$  0.32), the keto enol ether 24 ( $R_f$  0.52), the trienone 12 ( $R_f$  0.56), and two unidentified components ( $R_f$  0.64 and 0.75). Chromatography on silica gel with an EtOAc-hexane eluent (2:23 v/v) separated the crude diketone 17 as a colorless liquid that solidified on standing. Recrystallization from MeOH separated 353 mg (57%) of the diketone 17 as colorless prisms, mp  $99-100^\circ$ .

Table 5. Natural Abundance  $^{13}\text{C}$  NMR Spectrum of the Ketone 24  
in  $\text{CDCl}_3$  Solution

Signals in order of increasing field	$^{13}\text{C}$ nmr signal, ppm (multiplicity in off-resonance decoupling measurement) <sup>a</sup>
1	197.0 (s)
2	165.2 (s)
3	142.5 (s)
4	132.0 (d)
5	129.8 (s)
6	116.5 (s)
7	114.4 (s)
8	53.0 (t)
9 and 10	49.3 (2t)
11	43.8 (t)
12	42.1 (t)
13 and 14	40.7 (2t)
15	37.1 (q)
16	33.9 (s)
17	33.0 (s)
18	31.4 (s)
19,20,21, and 22	30.2 (2s,2q,?)
23 and 24	29.5 (2q,?)
25	27.2 (q)
26	26.1 (q)

<sup>a</sup>Where the multiplicity designation is accompanied by a question mark, the close spacing of two or more lines made the splitting pattern ambiguous.

An additional recrystallization from H<sub>2</sub>O-EtOH raised the melting point to 99.5-100.5°; ir (CCl<sub>4</sub>), 1665 (conjugated C=O), 1632, and 1600 cm<sup>-1</sup> (C=C); nmr (CCl<sub>4</sub>),  $\delta$  1.2-2.6 (19H, m, aliphatic CH), and 0.6-1.2 (21H, m, CH<sub>3</sub>); uv max (95% EtOH), 256 nm ( $\epsilon$  13,000); mass spectrum, m/e (rel. intensity), 396 (M<sup>+</sup>, 100), 381 (47), 340 (32), 325 (59), 307 (45), 201 (30), 141 (49), 83 (49), 69 (36), 55 (52), 43 (48), and 41 (61).

Anal. Calcd for C<sub>27</sub>H<sub>40</sub>O<sub>2</sub>: C, 81.76; H, 10.17.

Found: C, 81.73; H, 10.03.

After a solution of 200 mg (0.51 mmol) of the diketone 17 and 650 mg (16 mmol) of NaOH in 8 ml of MeOH had been refluxed for 15 hr under an N<sub>2</sub> atmosphere, the resulting dark yellow reaction mixture was concentrated and then partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. The ethereal layer was dried and concentrated to leave 180 mg of the crude product as a yellow solid, mp 144-147°; this material contained (tlc, silica gel coating with an EtOAc-hexane eluent, 1:9 v/v) the trienone 12 (R<sub>f</sub> 0.49) and a minor unidentified impurity (R<sub>f</sub> 0.53) but none of the starting diketone 17 (R<sub>f</sub> 0.25) was detected. Recrystallization from MeOH separated 154 mg (81%) of the trienone 12 as yellow prisms, mp 147-149°. This product was allowed to crystallize from EtOH very slowly to give 90 mg of the pure trienone 12, mp 149-150°, that was identified with the previously described sample by a mixture melting point determination and by comparison of ir, uv, and nmr spectra

When the natural abundance  $^{13}\text{C}$  nmr spectrum of the diketone 17 was determined in  $\text{CDCl}_3$  solution at ca.  $40^\circ$ , the six lines expected for the  $\text{sp}^2$  carbon atoms in structure 17 (Table 6) were accompanied by six additional less intense lines corresponding to a second conformer of structure 17. Because of the presence of two rotational isomers with different  $^{13}\text{C}$  nmr signals, we were unable to resolve satisfactorily the complex multiplet from the  $\text{sp}^3$  carbon atoms in this spectrum. To establish that these extra nmr signals arose from two slowly equilibrating conformers (presumably caused by restricted rotation about the C-C bond joining the two ring systems in structure 17, the  $^1\text{H}$  nmr spectrum of the diketone 17 in  $\text{PhCl}$  solution was examined at ca.  $35^\circ$  and at  $95^\circ$ . At ca.  $35^\circ$ , the highest field  $\text{CH}_3$  signal appeared as a less intense singlet at  $\delta$  0.68 and a more intense singlet at  $\delta$  0.74. When this solution was warmed to  $95^\circ$ , the two signals collapsed to a single line at  $\delta$  0.77; upon cooling this solution to ca.  $35^\circ$  the original spectrum was obtained.

#### Preparation of the Dimeric Ketols 38 and 39

The enone 37, prepared as previously described,<sup>24</sup> was obtained as a colorless liquid, bp  $89-98^\circ$  (16 mm),  $n_D^{25}$  1.4822 [lit.<sup>24</sup> bp  $84-86^\circ$  (9 mm)]; nmr ( $\text{CCl}_4$ ),  $\delta$  5.6-5.8 (1H, m, vinyl CH), 1.7-2.6 (8H, m, aliphatic CH), and 0.9-1.2 (3H, m,  $\text{CH}_3$ ). Employing a modification of previous procedures<sup>25,4</sup> a mixture of 100g (0.806 mol) of the enone 37, 300g NaOH, and 150 ml of  $\text{H}_2\text{O}$  was refluxed for 40 min and then



Table 6. Natural Abundance  $^{13}\text{C}$  NMR Spectrum of the  $\text{sp}^2$  Carbon Atoms in Diketone 17

Signals in order of increasing field	$^{13}\text{C}$ nmr signal, ppm (multiplicity in off-resonance decoupling measurement)
1	200.3 (s) <sup>a</sup>
2	198.7 (s) <sup>b</sup>
3	196.6 (s) <sup>b</sup>
4	194.6 (s) <sup>a</sup>
5	152.2 (s) <sup>a</sup>
6	149.8 (s) <sup>b</sup>
7	144.4 (s) <sup>b</sup>
8	143.6 (s) <sup>a</sup>
9	140.8 (s) <sup>b</sup>
10	139.9 (s) <sup>a</sup>
11	137.4 (s) <sup>b</sup>
12	137.1 (s) <sup>a</sup>

<sup>a</sup>Less intense signal.

<sup>b</sup>More intense signal.

poured into ice water and extracted with Et<sub>2</sub>O. After the ethereal extract had been washed with H<sub>2</sub>O, dried, and concentrated, the residual brown semisolid was triturated with cold hexane leave 46.5g of crude yellow solid.

Recrystallization from hexane afforded 37.0g (37%) of a mixture of ketols 38 and 39 (nmr analysis) as pale yellow needles, mp 96-110°. Fractional recrystallization from hexane separated 16.6g (17%) of the higher melting ketol 38 as colorless needles, mp 119-121° (lit. mp 116-118°, <sup>4</sup>120°<sup>1</sup>); ir (CCl<sub>4</sub>), 3470 (OH), 1650 (conjugated C=O), and 1627 cm<sup>-1</sup> (conjugated C=C); uv max (95% EtOH), 249 nm (ε 9100); nmr (CCl<sub>4</sub>), δ 4.93 (1H, s, OH) and 0.8-2.5 (23H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 248 (M<sup>+</sup>, 3), 191 (100), 121 (21), and 41 (11).

The hexane solutions from the trituration and the initial recrystallization were combined, concentrated, and distilled under reduced pressure in a short-path still to separate 34.8g of pale green viscous liquid, bp 118-135° (0.01 mm), that solidified on standing. Recrystallization from hexane separated 17.6g of colorless solid, mp 83-86° that contained (nmr analysis) both ketols 38 (minor) and 39 (major). A series of fractional crystallizations from hexane separated 1.49g (1.5%) of the pure lower melting ketol 39 as colorless plates, mp 90-92°; ir (CCl<sub>4</sub>), 3470 (OH), 1645 (conjugated C=O), and 1627 cm<sup>-1</sup> (conjugated C=C); uv max (95% EtOH), 248 nm (ε 8700); nmr (CCl<sub>4</sub>), δ 4.89 (1H, s,

OH) and 0.7-2.7 (23H, m, aliphatic CH); mass spectrum, m/e (relative intensity), 248 ( $M^+$ , 6), 233 (3) 191 (100), and 121 (20).

Anal. Calcd for  $C_{16}H_{24}O_2$ : C, 77.37; H, 9.74.

Found: C, 77.36; H, 9.77.

#### Preparation of the Dihydro Ketol 40

To a refluxing solution of 580 mg (76 mg-atom) of Li and 100 ml of  $Et_2O$  in 400 ml of liquid  $NH_3$  was added, rapidly with stirring, a solution of 5.35 g (21.6 mmol) of the ketol 38 and 5.0 ml of t-BuOH in 95 ml of  $Et_2O$ . After the reaction mixture had been stirred at  $-33^\circ$  for 45 min, 10 ml of  $H_2O$  was added and the  $NH_3$  was allowed to evaporate. The residue was partitioned between  $Et_2O$  and  $H_2O$  and the organic phase was washed with aqueous NaCl, dried, and concentrated. A cold ( $0^\circ$ ) solution of the residual semisolid in 50 ml of acetone was treated with excess aqueous 8 N  $H_2CrO_4$ , and then i-PrOH was added to consume the excess oxidant. After the resulting mixture had been neutralized with  $NaHCO_3$ , it was concentrated and partitioned between  $H_2O$  and  $Et_2O$ . The ethereal layer was washed with aqueous NaCl, dried, and concentrated to leave 4.96g of gray-green semisolid. Recrystallization from EtOH afforded 2.50 g of a mixture (ir analysis) of conjugated and nonconjugated ketones as a colorless solid. Chromatography on silica gel with an EtOAc-hexane eluent (1:6 v/v) separated 1.75 g (32%) of the ketol 40 as colorless needles, mp  $120-122^\circ$  (lit.<sup>1</sup> mp  $124^\circ$ );

ir ( $\text{CCl}_4$ ), 3550 (OH) and  $1700\text{ cm}^{-1}$  (C=O); uv max (95% EtOH), 294 nm ( $\epsilon$  25);  $^1\text{H}$  nmr ( $\text{CCl}_4$ ),  $\delta$  3.20 (1H, s, OH) and 0.6-2.8 (25H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 250 ( $\text{M}^+$ , <1), 232 (31), 217 (13), 193 (100), 175 (15), 125 (75), 124 (66), 111 (93), 109 (62), 108 (54), 107 (34), 83 (21), 69 (41), 55 (52), 43 (38), and 41 (53);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , multiplicity in off-resonance decoupling), 211.3 (s), 70.8 (s), 62.6 (d), 50.1 (t), 49.9 (t), 46.9 (t), 45.4 (t), 43.4 (t), 42.5 (t), 38.2 (d), 34.2 (s), 32.8 (d), 31.9 (q), 28.3 (d), 24.1 (q), and 22.0 (q).

#### Preparation of the Chloro Ketone 41

A solution of 511 mg (2.04 mmol) of the ketol 40 and 492 mg (4.14 mmol) of  $\text{SOCl}_2$  in 2.5 ml of  $\text{CHCl}_3$  (EtOH free) was stirred at  $25^\circ$  for 19 hr and then concentrated to leave 621 mg of red solid, mp  $89-91^\circ$ . Chromatography on silica gel with PhH as the eluent separated 494 mg (92%) of the chloro ketone 41 as a pink solid, mp  $93.5-94.5^\circ$ . Recrystallization from MeOH afforded the pure chloro ketone 41 as colorless plates, mp  $93.5-94.5^\circ$ ; ir ( $\text{CCl}_4$ ),  $1725\text{ cm}^{-1}$  (C=O); uv max (95% EtOH), 294 nm ( $\epsilon$  40);  $^1\text{H}$  nmr ( $\text{CCl}_4$ ),  $\delta$  3.33 (1H, d of d,  $J = 4.3$  and  $12.6\text{ Hz}$ ), 2.55 (1H, d,  $J = 12\text{ Hz}$ ), and 0.5-2.4 (23H, m, aliphatic CH); at 100 m Hz, the  $\text{CH}_3$  signals in the  $^1\text{H}$  nmr spectrum were resolved into a doublet ( $J = 6.1\text{ Hz}$ ) at  $\delta$  0.84, a singlet at 0.92, and a doublet ( $J = 5.6\text{ Hz}$ ) at 1.00; mass spectrum, m/e (rel. intensity), 232 (25), 217 (17), 125 (25), 124 (100), 111 (40), 109 (81), 108 (83), 107 (60),

105 (25), 93 (31), 91 (35), 79 (26), 77 (24), 69 (32), 67 (23), 55 (45), 43 (29), 41 (74), and 39 (27);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , multiplicity in off-resonance decoupling), 206.3 (s), 69.3 (s), 63.4 (d), 54.6 (t), 51.0 (t), 45.8 (t), 44.8 (t), 44.7 (t), 43.3 (t), 41.1 (d), 35.2 (s), 34.2 (d), 31.6 (q), 29.3 (d), 23.7 (q), and 22.0 (q).

Anal. Calcd for  $\text{C}_{16}\text{H}_{25}\text{ClO}$ : C, 71.49; H, 9.37; Cl, 13.19. Found: C, 71.48; H, 9.38; Cl, 13.18.

#### Preparation of the Amino Ketone 42

A cold ( $-33^\circ$ ) mixture of  $\text{NaNH}_2$  [from 340 mg (15 mg-atom) of Na], 1.00 g (3.73 mmol) of the chloro ketone 41, 125 ml of liquid  $\text{NH}_3$ , and 20 ml of THF was stirred for 5 hr during which time the  $\text{NH}_3$  was allowed to evaporate. After 5 ml of  $\text{H}_2\text{O}$  had been added, the reaction mixture was partitioned between  $\text{Et}_2\text{O}$  and aqueous NaCl. The ethereal layer was extracted successively with aqueous 1 M HCl and with  $\text{H}_2\text{O}$  and then dried and concentrated to leave 371 mg of colorless viscous liquid containing (tlc, silica gel with an EtOAc-hexane eluent, 1:9 v/v) the starting chloride ( $R_f$  0.58) and two unknown components ( $R_f$  0.0 and 0.74). The acidic aqueous extract was made basic (aqueous NaOH) and extracted with  $\text{Et}_2\text{O}$ . This  $\text{Et}_2\text{O}$  extract was dried and concentrated to leave 451 mg (49%) of the amino ketone 42 as a liquid that solidified on standing, mp  $69-71^\circ$ . Recrystallization from pentane afforded the pure amino ketone 42 as colorless prisms, mp  $72-73^\circ$ ; ir ( $\text{CCl}_4$ ), 3370 (NH) and  $1710\text{ cm}^{-1}$  (C=O);

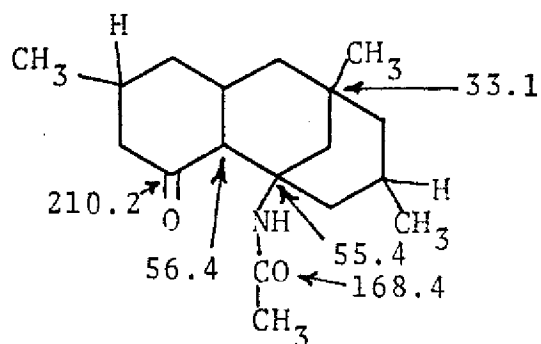
nmr ( $\text{CCl}_4$ ),  $\delta$  0.7-2.9 (m, NH and aliphatic CH); uv max (95% EtOH), 295 nm ( $\epsilon$  23); mass spectrum, m/e (rel. intensity), 249 ( $\text{M}^+$ , 3), 234 (5), 192 (65), and 124 (100).

Anal. Calcd for  $\text{C}_{16}\text{H}_{27}\text{NO}$ : C, 77.06; H, 10.91; N, 5.62. Found: C, 77.03; H, 10.95; N, 5.61.

#### Preparation of the Keto Amide 43

A solution of 52 mg (0.21 mmol) of the amino ketone 42 and 0.5 ml of  $\text{Ac}_2\text{O}$  in 1.0 ml of pyridine was stirred at  $25^\circ$  for 11.5 hr and then partitioned between  $\text{Et}_2\text{O}$  and aqueous 1 M HCl. The ethereal solution was washed with aqueous 5% NaOH, dried, and concentrated to leave 58 mg (95%) of the crude amide 43, mp  $134\text{-}135^\circ$ . Recrystallization from hexane separated the pure keto amide as colorless needles, mp  $135\text{-}137^\circ$ ; ir ( $\text{CCl}_4$ ), 3430 (NH), 1708 (C=O), and  $1672\text{ cm}^{-1}$  (amide C=O); uv max (95% EtOH), 293 nm ( $\epsilon$  25);  $^1\text{H}$  nmr ( $\text{CDCl}_3$ ),  $\delta$  5.68 (1H, broad, NH), 3.40 (1H, d,  $J = 13.2\text{ Hz}$ ), and 0.7-2.9 (27H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 291 ( $\text{M}^+$ , 33), 234 (49), 232 (55), 217 (31), 216 (34), 192 (68), 189 (77), 166 (57), 124 (100), 109 (42), 108 (45), 107 (38), 91 (34), 69 (41), 55 (51), 43 (64), and 41 (82). Although the  $^{13}\text{C}$  nmr spectrum ( $\text{CDCl}_3$  solution) of the keto amide 43 was complicated by restricted rotation of the amide C-N bond that caused a number of  $^{13}\text{C}$  signals to appear as two lines, the assignments indicated in the following formula are consistent both with off-resonance decoupling measurements and with the values observed for the

structurally related hydroxy ketone 40 and chloro ketone 41.



Anal. Calcd for  $\text{C}_{18}\text{H}_{29}\text{NO}_2$ : C, 74.18; H, 10.03; N, 4.81. Found: C, 74.08; H, 10.04; N, 4.79.

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